

Paul Lamek

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Spielberg

ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND
RELATED MATTERS.

Hearing held
8th floor
180 Dundas Street West
Toronto, Ontario

The Honourable Mr. Justice S.G.M. Grange

P.S.A. Lamek, Q.C.

E.A. Cronk

Thomas Millar

Commissioner

Counsel

Associate Counsel

Administrator

Transcript of evidence
for

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ROYAL COMMISSION OF INQUIRY INTO CERTAIN
DEATHS AT THE HOSPITAL FOR SICK CHILDREN
AND RELATED MATTERS.

Hearing held on the 8th Floor,
180 Dundas Street West, Toronto,
Ontario, on Thursday, the 27th
day of October, 1983.

- - - - -

THE HONOURABLE MR. JUSTICE S.G.M. GRANGE - Commissioner
THOMAS MILLAR - Administrator
MURRAY R. ELLIOT - Registrar

- - - - -

APPEARANCES:

P.S.A. LAMEK, Q.C.)	Commission Counsel
E. CRONK)	
D. HUNT)	Counsel for the Attorney
L. CECCHETTO)	General and Solicitor General
	of Ontario (Crown Attorneys
	and Coroner's Office)
I. J. ROLAND)	Counsel for The Hospital for
M. THOMSON)	Sick Children
R. BATTY)	
D. YOUNG	Counsel for The Metropolitan
	Toronto Police
W. N. ORTVED	Counsel for numerous Doctors
	at The Hospital for Sick
	Children
E. MCINTYRE	Counsel for the Registered
	Nurses' Association of Ontario
	and 35 Registered Nurses at
	The Hospital for Sick Children

(Cont'd)



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APPEARANCES: (Continued)

D. BROWN	Counsel for Susan Nelles - Nurse
E. FORSTER	Counsel for Phyllis Trayner - Nurse
J. A. OLAH	Counsel for Janet Brownless - R.N.A.
B. JACKMAN	Counsel for Mrs. M. Christie - R.N.A.
S. LABOW	Counsel for Mr. & Mrs. Gosselin, Mr. & Mrs. Gionas, Mr. & Mrs. Inwood, Mr. & Mrs. Turner and Mr. & Mrs. Lutes (parents of deceased children)
F. J. SHANAHAN	Counsel for Mr. & Mrs. Dominic Lombardo (parents of deceased child Stephanie Lombardo) and Heather Dawson (mother of deceased child Amber Dawson)
W. W. TOBIAS	Counsel for Mr. & Mrs. Hines (parents of deceased child Jordan Hines)
J. SHINEHOFT	Counsel for Lorie Pacsai and Kevin Garnett (parents of deceased child Kevin Pacsai)



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--- on resuming at 10:00 a.m.

STEPHEN PAUL SPIELBERG, Resumed

THE COMMISSIONER: Mr. Hunt.

MR. HUNT: Thank you, Mr.

Commissioner.

CROSS-EXAMINATION BY MR. HUNT (Continued):

Q. Doctor, I just want to go back to one matter we discussed yesterday afternoon before we broke.

A. Yes, sir.

Q. We were discussing the possibility of medication error during the resuscitation attempt.

A. Yes.

Q. You were, I think, in referring to the number of drugs that were administered, really drawing to our attention the number of opportunities that there were for administration error to take place; is that fair?

A. Yes.

Q. One thing I just wanted to ask you about - I don't know, do you have Justin Cook's chart?

A. No, I don't.

MR. HUNT: Mr. Registrar, it is Exhibit 116.

Q. It is on page 30 of that.



1

2

A. Thank you.

3

Q. Now, that is the list that

4

we have been referring to?

5

A. Yes.

6

Q. Do you have it there?

7

A. Yes.

8

Q. Now, the sample that was

taken --

9

THE COMMISSIONER: I'm sorry, what

10

page was it?

11

MR. HUNT: I'm sorry, Mr. Commissioner,

12

page 30.

13

THE COMMISSIONER: Oh, yes. Thank

you.

14

MR. HUNT: Q. The sample that

15

we were referring to as having been an ante mortem

16

sample that produced a reading of 72 or 78 nanograms --

17

A. Yes.

18

Q. -- as shown on page 57 of

19

that chart - do you see it there in the third column

20

over, 22nd of March?

21

A. Yes.

22

Q. The hour of collection noted

is 4:30.

23

A. Yes.

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Q. So that was collected at some point during the resuscitation efforts?

A. That is my understanding, yes.

Q. Now, if we go back to the list at page 30, we see that the time, or the approximate time, I suppose, of the injection of various drugs is noted there.

A. Yes.

Q. Would I be correct that, really, most of the drugs administered during this resuscitation attempt came after 4:30, according to the list?

A. Certainly, many of them did. Some came before and some were given before that.

Q. No question about that.

A. Yes, sir.

Q. It would appear, before 4:30, there was Inderal, atropine, morphine; atropine again, bicarbonate and adrenalin.

A. Yes, adrenalin.

Q. Now, in considering the number of opportunities that there were for drug administration error --



1

2

A. Yes.

3

Q. -- I take it it follows

4

that we have to discount any drugs that were

5

administered after the sample was collected because

6

we are taking our amount from the sample?

7

A. Presumably so, yes.

8

Q. Now, just before we leave

9

that, we were dealing as well with the efforts that
had been made by Dr. Costigan and Dr. Mounstephen

10

prior to the situation with Justin Cook arising,

11

where they attempted to lock up all the digoxin;

12

not just on 4A/B but all through the Hospital.

13

A. Yes.

14

Q. And there is a possibility

15

that you put forward that perhaps some digoxin was
missed and it could then have been involved in a

16

medication error.

17

I didn't have these yesterday when

18

we were speaking but I have them now. I will just

19

show them to you. These are two inventories of the

20

drugs that were made up by Dr. Costigan and Mrs.

21

Rappaport, and they are Exhibits 185, Mr. Commissioner,

22

which is Mrs. Rappaport's inventory, and Exhibit 205,

23

which is Dr. Costigan's and Dr. Mounstephen's

24

inventory.

25



1
2 Now, the evidence we have heard
3 on this point to date is that this inventory was
4 done by Drs. Costigan and Mounstephen on the Satur-
5 day night after eleven o'clock, between eleven and
6 one --

7 A. Right.

8 Q. -- or so.

9 A. Yes.

10 Q. Then, on the following day,
11 that is the Sunday morning, Mrs. Rappaport conducted
12 a further inventory throughout the Hospital.

13 A. Yes.

14 Q. And the evidence we have
15 heard with respect to Exhibit 205, dealing with 4A/B,
16 we have the adult and pediatric ampoules designated
17 by the size.

18 A. That should be .5; not .25.

19 Q. Okay.

20 A. It is an incorrect designa-
21 tion.

22 Q. All right.

23 In any event, it is then times 10,
24 indicating the number --

25 A. Yes.

Q. For each, and then 4A, it is



1

2

times 6 and times 8.

3

A. Yes.

4

Q. And that would then appear

5

that there were, in terms of ampoules on 4B on

6

Saturday night, 10 adult and 10 pediatric ampoules.

7

A. Yes.

8

Q. And on 4A, 6 adult and 8

pediatric ampoules.

9

A. Yes.

10

Q. Then, Mrs. Rappaport did

11

her inventory on the following morning, and that is

12

Exhibit 185, and we have her notation that, with

13

respect to 4A, she found 8 pediatric ampoules and

14

6 adult, and that corresponds with what Dr. Costigan

and Dr. Mounstephen found the night before.

15

A. Yes.

16

Q. And on 4B, she found 10

17

pediatric ampoules and 10 adult ampoules, which

18

corresponds with what they found before.

19

A. That is correct.

20

Q. I think, yesterday, you

21

had expressed some desire to know that sort of

information --

22

A. Yes.

23

Q. -- whether they corresponded.

24

25



1

2

A. Yes.

3

Q. And it would appear that,

4

if these are correct - and I suppose only the people who prepared them can attest to that - there was, in fact, the same amount found the next morning as they had found that evening prior to Justin Cook's death.

5

6

7

Would that be right?

8

A. Yes. There are other

9

things here that I don't quite understand as much.

10

For example, they found more adult ampoules on 4D

11

the following morning, which is an infant ward where

12

you wouldn't use it, you know. There are inconsis-

13

encies in the numbers which you expect in any kind of inventory, certainly.

14

Q. But so far as 4A/B are

15

concerned, there don't appear to be any inconsistencies?

16

A. No. But throughout the

17

others, there are indeed.

18

Q. Thank you.

19

Well, would you agree that, as we eliminate the various concerns that you have raised, quite properly, with respect to drug administration error at this point in time, as we eliminate them, the possibility of it having occurred during that point in time does decrease?

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A. It decreases in the quantity that is unquantifiable. I have no evidence for error, and I have no evidence for any other mechanism.

The issue with respect to error is high. We know a great deal about error. We know very little about administration. I cannot certainly, and I would not, pharmacologically, play one way or the other.

Q. I am not asking you to quantify it.

A. Yes.

Q. You agree it decreases but we can't quantify it in any --

A. I think one is left with a great deal of doubt and a great deal of inability to deal with it. For example, if you put digoxin --

Q. I don't want to cut you off but, you see, I have a time limit that I am being held to.

A. I'm sorry, sir. Please.

Q. My friends can pick up on the examples when it is their turn but I have to watch my clock.

Now, I would like to move to the question then of an intentional overdose.



1

2

A. Yes.

3

Q. And we have dealt in

4

considerable detail with medication error. I take

5

it -- you, I think, indicated error, in your

6

experience, occurs frequently; murder, in your

7

experience, doesn't occur so frequently, and that

8

enters into your assessment of the various possibilities?

9

A. Yes.

10

Q. I don't suppose that you -

11

maybe you have been involved in a situation involving

12

murder in a hospital before?

13

A. I have been involved in

14

situations where a drug was raised as a question of

15

murder, yes.

16

Q. But actual situations

17

involving murder in a hospital would be quite

18

A. Yes.

19

Q. If we could just assume

20

for a moment, in order to explore this possibility,

21

that that is what has occurred; that there has been

22

a murder of Justin Cook through an intentional

23

administration of an overdose of digoxin --

24

A. Yes.

25



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Q. -- I take it that for your
purposes your calculations don't change at all if
we accept that as a starting point?

A. With the variability that
we talked about and everything else, all we can do
is give maximum and minimum kinds of limits within
very broad categories.



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BB/cr

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In terms of the means or intent
the pharmacology to my way of thinking doesn't help
us, we can't separate on that basis.

Q. All right. Well, in
other words, you have taken some facts, you have
analysed them as best you can given that there were
unknowns?

A. Yes.

Q. And you have given your
best opinion with respect to quantities and times,
et cetera?

A. Yes.

Q. But they don't change
if instead of approaching it from the point of view
of drug error we approach it from the point of view
of murder?

A. Presumably not.

Q. Those calculations
stay the same?

A. Presumably not.

Q. So that you have said
that in your opinion the administration of the drug,
if that is what we are dealing with, and I take it
this is in either case, occurred at or shortly before
the time of arrest, which was at 4:20 in the morning?



1

2

2

A. Yes.

3

Q. Now, I appreciate that

4

picking a precise time like that is, you use that because that is something that is recorded somewhere?

5

6

A. Yes. Recognizing that

7

the ranges we are talking about in terms of timing have to be very broad indeed.

8

9

Q. Right. Now, with respect

10

to Justin Cook, before the arrest at 4:20 in the

11

morning we do see that there was a perhaps brief

12

period where it appeared there was some onset of the events that led up to the arrest at 4:20?

13

A. Yes.

14

Q. And I think it was at

15

3:45, which is only about 35 minutes before that

16

that according to the notes of Nurse Nelles, she

17

noted the baby appeared to be more cyanosed?

18

A. That is correct.

19

Q. Then there was a seizure.

20

The vital signs are referred to. I am looking at

21

page 29, Mr. Commissioner, and a Code 23 in fact

22

was called on the baby shortly after that point in time?

23

24

25



1 A. Yes.

2 Q. Once she began to notice
3 that?

4 A. Yes.

5 Q. And I take it inasmuch as
6 the arrest was at 4:20, when we talk about the
7 arrest we really have to talk about these events
8 that preceded that are I suppose obviously tied
9 to it that in estimating times, et cetera, you are
really considering this whole period?

10 A. One has to.

3 11 Q. All right. Your evidence
12 was that this administration of the drug, however
13 we are dealing with it, occurred at or shortly before
14 the arrest and we are now encompassing this brief
15 period of time before it as well where the events
16 appeared to be beginning to take place leading to
the arrest, is that correct?

17 A. Yes, but recognizing too
18 again that the further and further we go back the
19 more and more we have to begin talking about steady
20 state type phenomena which then again make the
21 probability of survival beyond that period of time
22 if we assume distribution less and less and less
23 likely and forces us back into the issue of more and
24 more and more vials which for the reasons we got into,
25



1
2 both the practical and the pharmacologic become less
3 and less likely.

4 But again, to be perfectly clear,
5 we have to deal with very broad limits because a
6 whole series of different pharmacologic constraints
7 can explain the same numbers.

8 Q. All right. So, bearing
9 in mind everything you have said with respect to
10 the broad ranges we are dealing with, in terms of
11 the administration - bearing in mind the broad
12 ranges, we are dealing with a timeframe of, from the
13 onset of these events to an arrest, that brief period
14 from 3:45 to 4:20, in that period or shortly before,
15 is that correct?

16 A. We are talking some time
17 in that general range, yes, sir.

18 Q. All right. And then you
19 have indicated that as one moves out past that
20 range back in time then it becomes much more difficult
21 to make these statements with any degree of
22 certainty?

23 A. Yes.

24 Q. And I think Mr. Lamek
25 in his examination in chief, and I am looking at
page 2198 of Volume 55, asked you whether it could



1
2 have been given as much as an hour before the death
3 or an hour and a half before the death and you have
4 indicated that that again becomes a case of guesswork.

5
6 A. Yes. And I think that is
7 a very fair statement.

8 Q. All right. So, as far as
9 you can take it without getting into guesswork, we
10 are dealing with that period 3:45 to 4:20 or shortly
11 before and not moving back from that to any
12 appreciable extent, is that correct?

13 A. In a general sense I
14 think that would provide the most reasonable
15 pharmacological explanations, albeit that one could
16 produce a model that could go further back.

17 MR. HUNT: Thank you, those are
18 all the questions I have.

19 THE COMMISSIONER: Thank you.
20 Mr. Young, you have no questions?

21 MR. YOUNG: No questions, Mr.
22 Commissioner.

23 THE COMMISSIONER: Mr. Ortved, you
24 have no questions?

25 MR. ORTVED: No, I have no
questions thank you, Mr. Commissioner.

THE COMMISSIONER: Thank you.



Spielberg, cr.ex.
(McIntyre)

2604

1 Miss McIntyre?

2 MS. McINTYRE: Thank you.

3 CROSS-EXAMINATION BY MS. McINTYRE:

6 4 Q. Dr. Spielberg, while we
5 have the case of Justin Cook fresh in our minds, I
6 have a few questions for you on that case as well.

7 A. Yes.

8 Q. I would like to have you
9 consider the possibility that one of the propanolol doses
10 given to Justin Cook was in fact digoxin. If we
11 can just look at the chart for a moment, it would
12 seem that propanolol was given to the baby on a
13 number of occasions that evening. Starting at
14 page 25 of the chart.

15 A. Yes.

16 Q. This is at approximately
17 6:20. I understand that he had a very severe blue
18 spell?

19 A. Yes. That is what appears
20 to have been happening and one of the treatments for
21 that is propanolol.

22 Q. Which in fact was given
23 by Dr. Jedeikin and he notes that there was an almost
24 immediate picking up following the giving of
25 propanolol at that time?

A. Yes, that is correct.



1
2 Q. Can you tell us very
3 briefly why propranolol would be given and what its
4 effect would be expected to be?

5 A. The drug itself is what
6 we call a beta blocking agent or beta adrenergic
7 blocking agent and what can happen in heart disease
8 such as this child had is that the heart begins
9 pumping against an obstruction that gets worse and
10 worse and worse going out to the pulmonary
11 circulation. So that the baby's ability to pump
12 against this obstruction, which is muscle getting
13 too tight in essence, decreases the ability of the
14 heart to deliver blood to the lungs to receive
15 oxygen.

16 What propranolol does is both
17 relax and aid in increasing the blood flow from the
18 baby's heart to the lung to allow for better oxygen
19 delivery. So, we are using it here to cause relaxation
20 of an apparent obstruction in blood flow.

21 Q. And I gather that it has
22 almost immediate effects, or at least it did on this
23 occasion?

24 A. Yes. Again, I can't give
25 you exact numbers. The general feeling is that after
an intravenous dose the effect is reasonably rapid,



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certainly within minutes.

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BB-B

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Q. Okay. Now, turning to page 14 I understand this is the doctor's order, the bottom order on the page. It would appear an order was made at that time, that is, at 6:30 in the evening for propranolol to be kept at the bedside, the bottom order?

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A. Yes.

Q. Okay. Now, I understand that from the evidence that Mr. Hunt reviewed with you that that would be in fact prior to the time that digoxin was locked up on the ward?

A. That would be my understanding, yes.

Q. Okay.

THE COMMISSIONER: I am sorry, can we go back. I thought it was locked up at 6:30 on the 21st. Was it not locked up on the 20th?

MS. MCINTYRE: I had understood it was some time between - Dr. Costigan was there some time between 9:30 and 1:30. That was the evidence of Mr. Hunt.

THE COMMISSIONER: Yes, the 21st is the Saturday?

MS. MCINTYRE: Yes. So that at



6:30 then when this order was made ---

THE COMMISSIONER: Yes, yes.

I wasn't concerned about the hour I was concerned about the day but it was the Saturday, was it?

MS. MCINTYRE: Yes, it was the 21st.

THE COMMISSIONER: Yes, all right.

MS. MCINTRYE: Q. Okay. And it is clear from page 27, the very last comment made by Sui Scott going off her shift that Inderal, which I understand is the same as propranolol, by the way.

A. Yes, Inderal is the trade name for the drug.

Q. Was placed by the bedside and she left at 7:30. So, by 7:30 - her note appears at the top of page 27 of the chart. The very last comment she says:

"Inderal 1 milligram in 1 cc at bedside."

A. Yes.



C/BN/ko

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Q. So we could assume that at that point there was what was thought to be propranolol at the bedside?

A. Yes, I think that is reasonable, yes.

Q. Now, at 3:45 it would appear Baby Cook had another blue spell?

A. Yes, the symptoms at least as best I can receive from the chart, again you would have to check with the cardiologists, my interpretation would be that the symptoms that he developed at 3:45 were extremely similar to the symptoms he had developed however many hours earlier, seven or eight hours earlier.

Q. And at that time the dose of propranolol that was left at the bedside earlier was administered?

A. Yes, I cannot quite read it.

Q. Well, if I can perhaps help you.

THE COMMISSIONER: What page are we on, Miss McIntyre?

MS. MCINTYRE: Q. Page 27. I am looking at Dr. Kantak's note about half way through where he says, the first word I actually cannot read. I think it is -- I am not sure: was given Inderal, .4



1

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millilitres to which he did not respond. Can you see that, Dr. Spielberg?

3

4

A. I have one place where it looks like gave .4 cc Inderal and then another .2 cc approximately five minutes later, and then there is something I cannot quite read.

5

6

7

8

Q. I am actually referring you to the note above that which is Dr. Kantak's note.

9

10

11

A. I am sorry, yes.

Q. And he says that .4 millilitres of Inderal given to which he did not respond?

12

13

A. Yes.

Q. And then apparently another .2 millilitres was given?

14

15

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A. Yes, there appears to have been a degree of -- I cannot again read it. It looks like a bradycardia shortly after the administration of the initial dose, and then following that the other events appear to have occurred, the administration of the atropine, the administration of the morphine, et cetera.

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Q. Right. Well, as I read this, the Inderal .4 millilitres did not seem to have any effect?

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A. Yes.



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Q. It did not have the same effect that it did when it was given earlier in the evening?

A. That is what the note would indicate, yes.

Q. Now, what I would like you to consider, Dr. Spielberg, is the possibility that that dose was not Inderal but was in fact digoxin, and can you tell me, first of all, whether if it was digoxin the clinical picture that follows would be consistent?

A. Well, again, we are stuck with the problem that both the heart disease and the drug can do very similar kinds of things. It appears the baby developed bradycardia after the injection. This could also be attributable to propanolol conceivably, since propanolol can act to slow the heart. It also is entirely consistent with administration of digoxin under those circumstances, either again from the vehicle initially, the propylene glycol which would cause an initial bradycardia or from the drug itself.

Clinically, I do not think we can separate out whether in fact it was Inderal or digoxin. The possibility exists that either could produce the same pattern and that the child's heart disease, again, would produce a similar pattern by itself, but it is consistent.



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Q. But on this occasion the
Inderal, if it was Inderal, did not seem to have the
same positive effect that it had earlier in the
evening?

A. That is correct.

Q. Now, as I understand from the
chart --

THE COMMISSIONER: I am sorry,
"Responded ...", what is that word?

MS. MCINTYRE: I am not sure to which
note you are referring.

THE COMMISSIONER: I am reading the same
one you were reading, I think, mid-way through that
note on the middle of page 27.

MS. CRONK: I think it is "partially",
yes.

THE COMMISSIONER: "Responded partially".

MR. ROLAND: Just before that I think it
says another .2 millilitres was pushed and then it says
responded partially.

MS. MCINTYRE: Q. Right, and then it
says responded partially.

A. Partially, and then his heart
rate drops, so very hard to really be able to figure
out the exact time sequence in there or exactly what



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was going on, again, consistent with all of the possibilities we have listed: the heart disease of the patient, potentially administration of an accidental dose or administration of the Inderal itself with failure in this case.

Q. In going to -- I take it that the arrest occurred approximately 35 minutes after that initial dose of propranolol was given?

A. Yes, that is my understanding.

Q. And that the resuscitation efforts were stopped at 4:56, which would have been slightly more than an hour after that dose of propranolol was given?

A. Yes.

Q. Can you please give me your view as to whether the findings of digoxin levels in this child would have been consistent with that dose at 3:45 being digoxin?

A. Again, within the broad constraints that we have talked about, it is consistent.

Q. In your evidence you have said that if the levels were taken in the distribution phase you would have estimated somewhere in the range of 350 micrograms?

A. Again, not knowing the central



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volume, and that is why I had to put up a range, for example, from 175 to 375 and then say we could go a little bit in either direction again because --

Q. Okay, it is somewhere in that area?

A. Yes, it is somewhere in that general neighbourhood.

Q. How would that correspond with the .4 millilitres of medication that was given at 3:45, which was believed to be Inderal?

A. Well, actually it is .6, I suppose, because we have to include the .4 and .2. That would be -- again if we are talking about adult strength digoxin we are talking in the neighbourhood of a hundred and some odd, .6 times 150, I suppose, micrograms, is that right, .6 times 250. I am little slow on calculating this morning. It would be about 150 micrograms, that neighbourhood.

The other thing one has to take into consideration with these very small volumes is that there is another .2 cc in the hub of the syringe, so that if somebody does one of the most common medication errors in pediatrics, which is to draw back a little bit of fluid from the line before injecting, then we have to talk about .8 millilitres instead of



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about .6 millilitres. Within those broad constraints, so then we are talking in the neighbourhood of closer to 200, 220 micrograms.

Q. So do I gather that would be consistent with what you had told us earlier on the ranges?

A. It is certainly not inconsistent, yes.

Q. Now, you have told the Commission quite a lot about medication errors. If in fact this medication was drawn up some time earlier in the evening at 6:30 or 7:30 and not administered until 3:45 in the morning, would that increase or decrease the possibility of error being made in your view?

A. Well, there is a problem when syringes are predrawn up in that one's confidence about what is in the syringe decreases because, again, you do not have the vial and the syringe there, so that the physician administering that drug is in a position where there is not the extra double check and triple check type phenomenon that we were talking about. So that if an error had been made initially and a syringe is hanging at the bedside with some sort of label on it, the extra checks that one would have



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to prevent an error from occurring are decreased so that the chance of an error occurring are proportionately increased.

Q. And if this medication had been obtained from another floor, in fact, would that have increased or decreased the possibility of error?

A. We cannot talk about that in the direct sense, but we certainly know that that is a bad practice. It means that somebody has to leave the ward in a rush, run over to another ward where they are not familiar necessarily where all the drugs are, perhaps interrupt people doing other activities; in a general sense it is a dangerous practice, yes.

Q. And if digoxin was in a vial or in a syringe at the bedside, could it be distinguished visually from Inderal?

A. If it were within the syringe --
THE COMMISSIONER: Sorry, from what, Inderal?

MS. MCINTYRE: Q. Inderal. Are digoxin and Inderal visually distinguishable?

A. No, if one had a 1 cc syringe filled with the drug, you would have a clear solution basically in each and there would be no way of telling.

Q. What if they were in a vial, do you know if the vials are distinguishable?



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A. All vials are distinguishable if you take the time to read the labels carefully and such, yes, but the vials could be mistaken as well.

THE COMMISSIONER: At least, just so that I will understand this, does it say how much was left?

MS. MCINTYRE: It is not clear from the note, Mr. Commissioner, I don't believe, how it was left. It just says: "Inderal at bedside".

THE WITNESS: Yes.

MS. MCINTYRE: And the order merely says, "Keep propalonalol by the bedside". It doesn't indicate specifically how it was kept, no; whether it was in a vial or whether it was predrawn into a syringe.

THE COMMISSIONER: We don't have this propalonalol among our exhibits, I take it?

MS. MCINTYRE: No, we don't. I had asked the Hospital if they could perhaps get one and maybe we will have one later in the morning.

MR. ROLAND: Mr. Commissioner, I think that will arrive later in the morning. We are also trying to get a picture of a vial of morphine. We can't provide you with a vial of morphine because it is a restricted drug.



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THE COMMISSIONER: I'm certainly glad to hear that.

MR. ROLAND: We will provide you with a photograph of one.

THE COMMISSIONER: All right.

Well, I don't want you to give evidence, Ms. McIntyre, but what is the usual procedure when you are told to leave it at the bedside? What do they leave? Do they leave --

MS. MCINTYRE: Well, perhaps Dr. Spielberg can tell us.

THE COMMISSIONER: You represent ten thousand nurses or something and I would think you could tell us.

MS. MCINTYRE: My understanding is that it was taped to the end of the bed, and I understand it is not usual procedure at all to do that.

THE COMMISSIONER: No, no. I am wondering, the form in which it was left, you see, if it was left in the vial, it would presumably be easier to tell than if it were put in the syringe.

I just wonder what is the usual procedure, that's all. I don't imagine you know the answer to that, do you, doctor? I would be surprised if you did.



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THE WITNESS: Well, in our hospital, it would vary. If it were drawn up - and sometimes we wish the drug to be drawn up so we can use it quickly - the rule was that the vial should also be taped there. Sometimes it was and sometimes it wasn't.

THE COMMISSIONER: Oh, I see.

MS. McINTYRE: Since the practice is unusual and certainly not proper from a nursing point of view, I can't really tell you, and I don't think it is clear in this case whether the vial was left or whether just a syringe was drawn up, and perhaps we will hear more evidence on that later.

Q. Now, Dr. Spielberg, I want to ask you some general questions about your evidence with respect to medication errors.

First of all, it would seem, from the studies that you have produced, medication errors occur in every institution in which they have been studied.

A. Absolutely.

Q. And that the variation that was found is between 5.3 per cent and 20.6 per cent of the institutions.

A. Yes, under 90 in adult systems, yes.



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Q. In fact, medication errors are a reality that we have to live with in large institutions?

A. We do everything we can to decrease them and, still, we are faced with them, yes.

Q. And the reason --

THE COMMISSIONER: Live or die with, I guess, as the case may be. I don't think that is a good expression, I don't think; that is something we have to live with; it may be a fact of life but we don't have to live with it.

MS. MCINTYRE: We have to try to reduce. It is a reality.

A. We struggle against it, yet, under the best of circumstances, it still happens, yes.

Q. And the reason that nurses are the ones who are frequently involved in medication errors is that, as a general rule, it is a nursing function to administer medication?

A. Yes. In fact under the system which existed at the Hospital at that time, not only did the nurses have to administer the medication but they also had to prepare them, because there was no pharmacy providing syringes prefilled for



D5

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2 each child. This obviously is one of the reasons
3 that medication errors are higher in non-unit dose
4 systems, particularly when nurses have to spend a
5 great deal of their time -- my understanding is it
6 could run, you know, perhaps a quarter of their time
7 doing nothing but going and getting and preparing
8 medications. Many studies looking, for example,
9 at error rates, nurses trying to calculate doses or
10 provide vials compared to pharmacists in a
11 general sense, because pharmacists are trained
12 specifically to deal with drugs. Drugs prepared in
13 the pharmacy do have a less likely possibility of
14 error than drugs prepared by nurses on the wards
15 since the nurses' responsibilities, generally, are
16 directly to the patient at bedside and preparing
17 drugs takes them away from that.

18 Q. And nurses are involved
19 in all sorts of other duties at the same time as they
20 are preparing medications?

21 A. Exactly.

22 Q. Therefore, they don't have
23 the concentration that a pharmacist may have in
24 preparing medications?

25 A. Yes. And this is complicated further in pediatrics by the fact that nurses not



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only have to do standard vital signs; they also have to feed the infants, change the infants, comfort the infants; so the time required and the overall time spent by nurses in intensive involvement with the patients in pediatrics almost has to be greater than in adult medicine and, as such, the necessity of preparing medications becomes all the more difficult.

Q. But I take it that nurses are not alone in making errors; that pharmacists also make errors --

A. Certainly.

Q. -- in calculating and preparing medication?

A. Absolutely true.

Q. And physicians make errors as well in ordering --

A. Yes.

Q. -- in ordering a wrong dose --

A. Yes.

Q. -- or errors in administration?

A. Yes.

Q. If they are administering



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the medication.

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A. Yes, exactly.

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Q. And it is not a reflection

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on the nursing staff if medication errors occur;

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that you can have the best possible nursing staff

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and you are still going to have medication errors

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made?

A. Yes, that is true.

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The only studies that have tried

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to look at that were one study in a newborn ICU,

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looking at very experienced nurses and very in-

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experienced, or new graduates, in terms of the kinds

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of errors made in calculation, for example, in this

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situation.

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In fact, the more rushed the

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situation, basically both groups were performing

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pretty much equally, so that, even despite the fact

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that the more experienced nurses were far better

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nurses, well-trained, well-experienced; nonetheless,

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errors are made and, basically, it is a fact of life

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among all health professionals throughout the world.

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Q. I take it from your evidence

that much can be done to reduce the percentage of

medication errors --

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A. That is correct.

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D8

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Q. -- by making improvements

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in the system?

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A. That is correct.

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Q. As I understand it, the

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unit dose system makes a substantial improvement

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because the doctor's order, as a rule, goes to the

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pharmacy where it is filled and the prepared doses

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are then sent back to the ward for the individual

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patient?

A. Yes, that is correct,

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with the patient's name, the volume and the concentra-

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tion of the drug in question on the label.

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Q. But during the period in

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question before this Commission; that is, from July

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1980 to March 1981, there was no unit dose system

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in place?

A. Yes, that is my understanding.

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Q. So that the nurses would have

18

to not only prepare the medications but they would

19

transcribe the doctors' orders into their nursing

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records?

A. Yes.

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Q. And that is subject to a

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lot of errors, would you agree?

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A. Yes. Certainly, the more

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D9

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2 steps required along the way, the more possibilities
3 of, for example, simple misinterpretation of hand-
4 writing; these kinds of things. Each time along the
5 way an additional step is required before it finally
6 gets to the right source, the potential for error
is increased.

7 Q. And I take it that, in many
8 cases, a nurse would have to calculate the doses
9 from the orders that the doctors gave?

10 A. Yes. One of the problems
11 we struggle with in pediatrics again, particularly,
12 is that the volumes we are talking about very often
13 are quite small; so that small errors in volume,
14 for example, you know, instead of .1, 1 cc. becomes
15 a tenfold error by moving a decimal place. If an
16 order is written in milligrams, for example, then
17 the nurse has to calculate from milligrams to the
18 number of millilitres of that drug, which requires
19 a calculation, for many medications, for example
20 at Johns Hopkins, when I was there, we were having
21 multiple problems resulting from just those kinds of
22 things with drugs, for example, like chloramphenicol
23 where the calculations were not shown on the medica-
24 tion record; only milligrams were given. We had
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D10

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2 multiple errors with the drug and, as a result,
3 required the House Staff, in writing the orders, to
4 put not only milligrams but millilitres as well and
5 show the calculations. That is an optimal kind of
6 system for trying to decrease errors, particularly
7 in pediatrics, where each child is getting a different
8 dose.

9 Q. I understand that some
10 systems also require that only generic names of drugs
11 are used rather than the manufacturer's brand name.

12 A. Yes, that is true. Again,
13 because of potentially name confusion, since many
14 drugs, particularly the trade names, tend to be
15 shortened and tacky-type names, and many tend to
16 resemble each other.

17 Q. I understand that, on 4A/B,
18 there was also a problem - and I don't know whether
19 you know anything about this in terms of the medication
20 trays that the nurses had for distributing medications
21 to the patients after they were prepared - that there
22 was not enough -- there was no appropriate space on
23 the trays for syringes.

24 Do you know anything about that?

25 A. I am not directly aware of
that.



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Q. So that the syringes had to be carried in a group on a tray and could easily be confused. You don't know anything about that?

A. No. Certainly, though, if you have a stack of syringes together, that is again a potential for a problem, yes. I don't have firsthand knowledge of precisely how the drugs were being administered at that time.

Q. I take it from the Dubin Report, in which there is reference to a lot of problems with respect to medication procedures - I note that, under the Dubin Report, medication errors is discussed under the Pharmacology Department.

Is it the Pharmacology Department that is primarily responsible for establishing medication procedures?

A. No. It is the Department of Pharmacy --

Q. Oh, I am sorry.

A. -- that is directly responsible for such.

Q. I see. And they have to, of course, cooperate with the nurses who are administering the medication?

A. Yes.



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MS. McINTYRE: Thank you. I have
no further questions.

THE COMMISSIONER: Thank you, Miss
McIntyre.

Miss Jackman.

MS. JACKMAN: No questions, Mr.
Commissioner.

THE COMMISSIONER: Mr. Olah.

MR. OLAH: Thank you, Mr. Commissioner.

MR. ROLAND: Mr. Commissioner,
before Mr. Olah commences, we now have a 1 millilitre
vial of inderal¹, which is propranolol, and perhaps
the witness could identify it.

THE WITNESS: Yes, that is correct.

THE COMMISSIONER: It is called
inderal?

MR. ROLAND: Inderal, injectible.
I-n-d-e-r-a-l.

THE COMMISSIONER: Do you want to
see that? It is put in with - what number is that?

MR. ROLAND: It is put in with
Exhibit 225.

In addition, we have four photo-
graphs that were taken this morning and they are our
best effort, given the constraints of the apparatus



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D13 2 itself, which couldn't get closer than about 3 ft. to
3 the vials, but they show various kinds of vials and
4 identification of them is on the back of the photo-
5 graphs, each of the photographs.

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MR. ROLAND: The issue, among other things, various vials of morphine. These photographs are the best we can do for you with respect to morphine and there are four different sizes of dosage in, I think, two millilitre vials of morphine. Perhaps we can have those marked.

THE COMMISSIONER: Just to refresh me, what is the relevance of the morphine?

MR. ROLAND: Well, there was morphine administered to Baby Cook.

THE COMMISSIONER: Oh, all right.

MR. ROLAND: Shortly before the arrest.

THE WITNESS: Yes. The second point being that, at least to my understanding, the digoxin was locked up in a narcotics cabinet, which is an unusual place to keep a drug like that. It was certainly an unfamiliar place to keep a drug like that and it would have been stored near the other narcotics so that, again, if we are thinking of the potential of error, here is a drug such as digoxin in a place where it normally isn't, sitting next to morphine.

MR. ROLAND: And, Doctor -- I'm sorry, it isn't my turn to ask questions about that, but since we are on the subject, how large is that



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2 cabinet that is locked up?

3 THE WITNESS: That I don't know.

4 MR. ROLAND: You don't know. All right,
5 fine. Perhaps I can have these marked as the next
6 exhibit, Mr. Commissioner.

7 THE COMMISSIONER: Have you seen these?

8 THE WITNESS: No, I haven't.

9 THE COMMISSIONER: Would you like to
10 take a look at them?

11 THE WITNESS: Sure.

12 THE COMMISSIONER: I have absolute faith
13 in Mr. Roland but not as a pharmacologist. I think
14 we will wait just for a moment, Mr. Ola, and see.

15 THE WITNESS: Yes. They are a little
16 bit hard to read but, in essence, that is a bit
17 realistic to that extent.

18 THE COMMISSIONER: Yes, all right.
19 What is the number?

20 THE REGISTRAR: Exhibit 228.

21 MR. ROLAND: Perhaps we can mark
22 them A, B, C and D.

23 THE COMMISSIONER: Yes, all right, A,
24 B, C and D.

25 THE WITNESS: Yes. These look like
reasonable pictures, as best I suppose we can do under



the circumstances.

THE COMMISSIONER: All right.

MR. ROLAND: We will mark as A a photograph that shows five different vials, one of digoxin and four of morphine.

---EXHIBIT No. 228-A: Photograph showing five different vials, one of digoxin and four of morphine.

MR. ROLAND: And is B a photograph showing three vials, one of digoxin, one of morphine and one of inderol.

---EXHIBIT No. 228-B: Photograph showing three vials, one of digoxin, one of morphine, one of Inderal.

MR. ROLAND: And C is a photograph of three vials in that the same three vials are the same three vials as in the last photograph, but they are in a different order, this time Inderal, morphine and digoxin.

---EXHIBIT No. 228-C: Three vials, Inderal, morphine and digoxin.



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2 MR. ROLAND: D is a photograph of four
3 vials, digoxin, lasix, Valium and morphine.

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5 ---EXHIBIT NO. 228-D: Photograph of four vials:
6 digoxin, lasix, Valium
7 and Morphine.

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9 THE COMMISSIONER: I had better just
10 take a look at those.

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12 MR. OLAH: You need a magnifying glass
13 to see those, Mr. Commissioner.

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15 THE WITNESS: In real life, too, often.

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17 THE COMMISSIONER: At least, Mr. Olah,
18 we don't have a stopwatch on you yet.

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20 MR. OLAH: It probably doesn't matter,
21 the kind of questions I ask

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23 THE COMMISSIONER: I can't see anything
24 in these.

25
THE WITNESS: It is the reverse side.

THE COMMISSIONER: Yes, all right. All
right, Mr. Olah.

MR. OLAH: Thank you, Mr. Commissioner.

CROSS-EXAMINATION BY MR. OLAH:

Q. Doctor, I would like to go
back to the theme that seemed to develop in your
examination with Mr. Lamak and also with Mr. Strathy
yesterday and that was the discussion you had with



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2 both of them with respect to pathophysiology.

3 A. Yes, sir.

4 Q. I think you indicated that when
5 the child, Gary Murphy, died, you were very concerned.

6 A. Yes.

7 Q. And the first thing that leapt
8 into your mind was some sort of administration,
9 either accidental or intentional, and it was only in
10 1983, very recently, with the new development and
11 literature and medical science that you were able to
12 explain the fairly high readings in that child by
13 some means other than administration.

14 A. That is correct.

15 Q. The impression I got, Doctor,
16 and please correct me if I am wrong, is that there
17 have been some really very new and radical develop-
18 ments in this area pertaining to digoxin and what
19 happens in the body in certain situations, illnesses,
20 of the kind you mentioned.

21 A. Yes, I think that is a fair
22 statement.

23 Q. It almost appeared as though
24 in certain areas of digoxin knowledge you gentlemen
25 seemed to be on the frontiers of medical science.

A. What we are talking about from



6 1
2 the literature is certainly not our work, this is
3 work being done by others.

4 Q. By you gentlemen I mean doctors
5 and pharmacologists.

6 A. I think what is happening now in
7 a broad sense is a re-examination of much of what
8 we had felt reasonably quote "happy about"
9 with respect to the drug and in fact both in terms
10 of its therapeutic use we are now approaching the
11 drug very differently, we are asking new questions
12 about the way in which it works in some children with
13 heart disease because new information is coming out
14 in that area and a tremendous amount of new informa-
15 tion is coming out with respect to the relevance or
16 perhaps lack of relevance of blood levels in
17 therapeutic practice or in other pursuits.

18 Q. This is all very new and fairly
19 radical, as I understand it, and alters your percep-
20 tion of the drug and the manner it works and the man-
21 ner it should be treated or handled.

22 A. I believe we have had to rethink
23 a great deal, yes.

24 Q. And, of course, this is not
25 unusual in science or even in medical science because
that is how science develops, theories are developed,



7 1
2 facts don't fit into theory and then new theories
3 have to be developed to explain those new facts that
4 occur.

5 A. That's correct. To give you an
6 example, theophylline, which is a drug that every
7 pediatrician uses for asthma, I was taught in medical
8 school that its major mechanism of action was inhibit-
9 ing a specific enzyme and that's how it caused
10 bronchodilatation in opening the breathing tubes
11 during asthma. That happens in the test tube very
12 well. It now turns out that there are other multiple
13 other ways in which theophylline works, including
14 helping the diaphragm to work more efficiently,
15 things that we knew nothing about, which change our
16 whole approach to thinking about these drugs and
17 the development of new drugs and I'm never surprised
18 by that.

19 Q. In effect, what has happened, as
20 I understand you to be saying, is that it is now
21 possible to explain in a medical sense and in an
22 innocent sense digoxin readings, post-mortem
23 readings in the range of 20 to 30 nanograms.

24 A. There have now been instances
25 where that has been the case.

Q. And I detected a note of caution



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2 or concern as you were testifying that your
3 concern is that in the next several years it may be
4 that there is some other explanation that will emerge
5 as a result of further research in this area that
6 may offer an innocent explanation in certain cases of
7 readings substantially higher than that, than that
8 range of 20 to 30.

9 A. I think we have to keep that
10 in mind, as much as our concern is keeping in
11 mind that somebody may in fact have given intentional
12 overdoses. I think our concern is that we must, at
13 least as pharmacologists and scientists, keep a very
14 broad mind to what is developing, what new things
15 are coming out and how that may change our interpreta-
16 tion of old data.

17 Q. And of course parallel to this
18 research into digoxin and its reaction on the body
19 in psychokinetics -- I'm sorry, pathopsychology.

20 A. Physiology.

21 Q. Physiology. I should have gone
22 to medical school before we came here, Doctor. You've
23 got parallel research going on into what has been
24 called endogenous digoxin-like substances and from
25 what Dr. Soldin has said we now have three drugs in
three different substances, apparently, X, Y, and Z as



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2 he called them. So that this whole area seems to me
3 as a layman, and I am only approaching it as a
4 layman, seems to be in a state of sort of explosion,
5 if I may put it that way.

6 A. Well, to put it in a scientific
7 construct, were we not faced with the tragedy that
8 we are faced with now, this would be such an exciting
9 area of research we would all be very joyous about
it.

10 Q. Doctor, I apologize, I should
11 have told you why I am here and who I am. I act on
12 behalf of one of the registered nursing assistants
on the three nurse team.

13 A. I see.

14 Q. And I would like to take our
15 dialogue to a different area at this time, if I
16 may. I would like to deal with three specific
17 children, if I may.

18 A. Yes.

19 Q. Pacsai, Inwood and Hines.

20 A. Yes.

21 Q. As I understood your evidence
22 over the past couple of days, assuming, and for
23 purposes of this discussion for the next few minutes,
24 I would like you to assume an intentional administration
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of digoxin.

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A. Yes.

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Q. Do I take it that in certainly the

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two cases that you are familiar with, Pacsai and
Inwood.

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A. Yes.

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Q. Assuming that hypothesis I put

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to you, your explanation for the administration of

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the drug would be during the alpha phase. We are not

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talking about the beta phase.

11

A. Yes. With the situation

12

certainly with Baby Inwood ---

13

Q. Maybe we should talk about one

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child at a time. Let's talk about Inwood.

15

A. Yes, I think we had better be-

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cause the issues are somewhat different. With
Kristin Inwood the extraordinarily high reading, again,

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if we accept that it is not artefactually high,

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would mitigate very much towards a pre-distributive

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type of phenomena, the alpha phase, very acute

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administration type phenomena.

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Q. Right. So, we can exclude the

beta phase all together.

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A. It becomes very unlikely with

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readings that high, yes.

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2 Q. All right. I guess, like a good
3 scientific man, you can't talk about certainty
4 because there is no certainty in science.
5 A. I cannot.
6 Q. But if we are talking about
7 probabilities we are talking a very high order of
8 probabilities that we are into an alpha phase
9 situation, are we not?
10 A. That is what I would interpret
11 the number to be, yes.
12 Q. We are talking something in the
13 order of 95% certainty, would that be fair?
14 A. I wouldn't even want to go that
15 far, really.
16 Q. All right.
17 A. We cannot, basically, because
18 we are lacking the information.
19 Q. May I just ask you this question,
20 then, and please come back with the response you want.
21 A. Yes.
22 Q. Would you say that of all the
23 things that we can estimate or guesstimate in these
24 proceedings, that is one of the few things that we
25 can be fairly certain about, that certainly in the
case of Kristin Inwood, assuming that there is an



12 1
2 accurate reading of 491 that we are in the alpha
3 phase.

4 A, I think that is a very, very
5 good assumption, yes.

6 Q. All right.

7 A. Based on everything that we have
8 gone through. And again, assuming that that number
is correct.

9 Q. I understand your reservations
10 about the reading. Now, as I understand, you break
11 up the alpha phase into three separate sort of compo-
12 nents. Firstly, you have immediately prior to
13 arrest, secondly at the bottom end of the alpha
phase is the constant state or the steady state.

14 A. Well, I wouldn't quite define
15 it that way, no. I think really what we are talking
16 about in terms of an alpha phase is a slope from a
17 central compartment down to the steady state.

18 Q. Well, if I may just put it
19 on the board. As I understood it, and please
20 correct me if I am wrong, this is the alpha phase.

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F 1
BN/cr 2 If an injection or an administration
3 of digoxin occurs at the top of the scale, that
4 would be something immediately prior to arrest, would
5 it not?

6 A. If we were going to be
7 strictly pharmacologic about it, we would have to
8 talk really about a three compartment model under
9 those circumstances. So the first issue is
10 immediately after injection with cessation of
11 circulation. Then we enter ---

12 Q. I am sorry, that would
13 be, what do you call the first phase?

14 A. For lack of a better term
15 let us call it pre-alpha.

16 Q. Pre-alpha. That really
17 denotes an administration at the very top of the
18 phase?

19 A. Exactly, with the drug
20 basically not leaving circulation.

21 Q. All right. At the bottom
22 of the phase right here ---

23 A. We have reached steady
24 state.

25 Q. Steady state.

A. Yes, and the curve between



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BN/PS 2

those points is then the alpha phase.

3

Q. Or distribution?

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A. Yes.

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Q. I apologize for my writing.

6

Lawyers are as bad as doctors.

7

Now, what I would like to do is put
some time ---

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THE COMMISSIONER: Those are not
divisions of the alpha phase, though. Distribution is
the whole thing.

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MR. OLAH: Yes, is the whole thing, but
what I would like to do, Mr. Commissioner, if you
would bear with me ---

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THE COMMISSIONER: Sorry, Mr. Roland?

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MR. ROLAND: Mr. Commissioner, yes,
I did not want to be too critical of Mr. Olah's
artistry, but the witness has put in Exhibit 217-1
that gives his artistry of the graph, and I think
it is somewhat different than Mr. Olah's, and to
be fair to you and to the witness, that has already
been put in.

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THE WITNESS: Yes.

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MR. OLAH: I am not trying to do any-
thing magical here.

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THE COMMISSIONER: But the thing is I



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do not believe that it ever was described as the
alpha phase divided into three.

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THE WITNESS: No, I think that is probably
not a good construct.

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MR. OLAH: Q. All right. Well, then,
let's abandon the construct.

7

8

A. Because it is getting a bit away
from what we would standardly view as kinetics and ---

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Q. What I am trying to get at is
this: I am trying to establish time parameters.
Would it be fair to say that since in the Inwood
situation we have eliminated the beta phase, that the
maximum time that an intentional administration could
have occurred would have been two and a half
hours prior to arrest?

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A. Again, we cannot really deal
with that in that sense. If what we are saying
is that in all likelihood a number that high
has to be up somewhere reasonably high on the alpha
distribution phase or even above that, i.e., still
within circulation, then we are talking about
reasonably short periods of time. If we are talking
two and a half hours, we have already totally
distributed that drug.

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Q. I know, Doctor, and that is not



4 1
2 the point I am making. Just try to help me in the
3 point I am trying to get at. Being a layman, it is
4 difficult to ---

5 A. Yes, I do not quite understand
6 the question.

7 THE COMMISSIONER: You have to make
8 another assumption. There has to be only a certain
9 amount of the drug injected, so you have to make
10 that assumption before your answer will become valid.

11 MR. OLAH: That is true, and I apologize.
12 We are assuming a certain intentional administration
13 of medication in the child Inwood, just for the
14 purposes of our discussion. That is the premise we
15 are operating on.

16 What I am trying to define, Doctor, and
17 maybe this might be the better way of approaching
18 it, is what is the absolute outside maximum time in
19 which an administration, an intentional administra-
20 tion could have occurred, assuming or bearing in mind
21 that we have pretty well eliminated the beta phase
22 in this case.

23 THE COMMISSIONER: But do you not
24 have to define the amount as well?

25 THE WITNESS: Precisely.

THE COMMISSIONER: You have to add that



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to the equation before it makes any sense.

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MR. OLAH: Well, I do not think so,
Mr. Commissioner.

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THE COMMISSIONER: Well, the witness
will tell me if I am wrong but ---

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MR. OLAH: I do not know. I am
struggling and ---

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THE COMMISSIONER: If you assume one
adult vial, for instance, if you assume one adult
vial and assume the alpha phase, then you can ask
the witness reasonably at what point would that
have to be administered and he can answer it, but
I do not see how he can answer if you do not
assume the amount that is given.

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MR. OLAH: I understand your concern
and I am not asking for specific times. What I am
trying to define is the maximum outer time limit in
which any dose could have been -- a very large
dose could have been administered, bearing in mind
that my client had been absent some seven and a
quarter hours, and I suspect that the very outside
limit is going to be something substantially less
than seven and a quarter hours, and that is really
what I am trying to define.

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THE COMMISSIONER: Well, I would have



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1
2 thought that for your purposes you would assume that
3 it was administred seven and a half hours before,
4 what quantity would have to be administered in order
5 to create that result, or could it be. However, I
6 must not tell you how to do it.

7 MR. OLAH: I suspect I may be able to
8 get a more favourable response than that and it may be
9 of assistance to everyone concerned.

10 Q. Do you see the point I am trying
11 to make, Doctor? We have already eliminated the beta
12 phase. If we are assuming the maximum time back
13 from the arrest for an administration, what is the
14 maximum time limit or outer limit that you can ascribe,
15 bearing in mind the situation?

16 A. Well, you know, again I think
17 we do have to take the concerns the Commissioner has
18 raised into consideration.

19 Q. Let us assume a very large does.

20 A. But again, the trouble is very large
21 doses have a broad range. Let me try with the kinds
22 of things we are talking about is more reasonable,
23 you know, single adult vial type considerations, okay.

24 THE COMMISSIONER: Well, I wonder if I
25 can help you a bit on this.

MR. OLAH: I would be grateful.



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THE COMMISSIONER: There is no question that if it is in the alpha phase we are going to have to be two and a half hours ---

THE WITNESS: Yes, two and a half to four hours.

MR. OLAH: All right, two and a half to four hours is the maximum time phase that a very large dose could have been administered in the alpha phase?

A. If it were still being distributed, yes.

Q. If it were still being distributed.

A. Yes, sir.

Q. All right. So four hours is the maximum in the distributive phase?

A. That is the literature published maximum. Again, we are going to have to add in any given infant distribution might be longer or might be shorter. That is not an unreasonable estimate from everything we know.

Q. Now, similarly, I assume in the Pacsai case what kind of maximum sort of time zone can we draw in the Pacsai case, bearing in mind that the arrest occurred at 8:45 a.m.?

A. As I indicated yesterday ---



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Q. Again, on the same assumption,

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Doctor.

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A. Yes, well, except that we cannot

5

really use that assumption in this case very well

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and that is the problem we have with Kevin and

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why we had to think about alternate ways that the

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blood level could be, say, ten or greater. During

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his ICU stay he still goes back into sinus rhythm

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and then deal with a 26 postmortem, which is very

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reasonably consistent with a ten or greater four

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hours later. So I do not think we can talk about

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Kevin being on an alpha phase of distribution. The

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ten or greater than ten and 26 fit very well with

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what we know to date about pre and post mortem and

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that is why we had to get into the issue of could

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that ten be a steady state, and if it is at steady

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state, then it does not fit well with administra-

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tion because in fact here is a child with terribly

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bad arrhythmia problems who has already demonstrated

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that he had functionally died at St. Joseph's and

22

been resuscitated and had had several other ar-

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rhythmias. Then it becomes very difficult to postu-

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late how the ten could be steady state from administra-

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tion, and yet, the numbers make it difficult to think

about that being on an alpha phase because the baby



1
2 was back in sinus rhythm and presumably would have
3 been distributing drug afterwards.

4 That is why in that situation we had
5 to invoke the very high probability that we are
6 dealing with a pathophysiologic situation which,
7 again, we do not pretend to understand at this
8 point, but which might in fact explain both his
9 primary disease and the digoxin readings.

10 If we have to think about exogenous
11 administration of drug in that baby, I am not
12 sure how to cope with it, frankly.

13 Q. What you are saying is -- let
14 me see if I understand it -- because of the pre-
15 existing condition of this baby, anything larger
16 than ten nanograms antemortem, you would have
17 expected death to occur and he would not have
18 survived as long as he did?

19 A. If that was, for example,
20 digoxin administered to the baby, yes. If it was
21 dedistributing from other tissues, then it might not
22 have caused any toxicity whatsoever.

23 Q. Sure, I understand, and that is
24 why you rule out an alpha phase situation in the
25 Pacsai baby?

A. I find it much, much harder to



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deal with because he was in the ICU for such a long time.

Q. But if you happen to be in error and it is an alpha phase situation, then again we are talking about a maximum of four hours or so?

A. That is the kind of constraints we are talking about, yes, and I have to add in something like that is also a possibility; I cannot rule it out.

Q. Sure, I understand that. My job is to rule out every possibility that militates against my client, Doctor.

A. I understand.

Q. So here we have got an arrest of 8:45 a.m., so assuming this very small possibility, in your view, of administration on an alpha phase, that would have occurred at about 4:45 a.m. maximum?

A. I am sorry, what time was he transferred to the ICU?

Q. Six o'clock in the morning.

A. He was transferred at 6 o'clock in the morning. Okay.

Q. Yes, again, we are trying to define the maximum outer perimeters.



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A. If we are talking about an alpha distribution phase, then again we can talk about two and a half to four hours prior to that 6 a.m. if that is the hypothesis.

Q. So the very outside time limit under an alpha phase under that hypothesis is about 4:45 a.m., subtracting four hours from 8:45?

A. Well, no, the greater than ten, though, is taken ---

Q. At about between 6 and 6:30 in the morning.

A. It was between 6 and 6:30, so we have to go back from that time, if you will.

Q. All right. So then let us go back and we are talking about 2 o'clock in the morning.

A. Yes.

Q. So if my client was off about 7:30 in the evening, that certainly would exclude her under that hypothesis?

A. Under that specific hypothesis.

Q. Now, Mr. Lamek also posed another hypothesis to you, Doctor, and that was an oral administration; do you recall that?

A. Yes.



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Q. And that in fact Baby Pacsai was peaking at the time the 6:30 reading was taken.

A. Yes.

Q. If there is an oral administration, what kind of an outside maximum time parameter are we talking about?

A. As we indicated, the standard peaks, again, assuming that everything is working right and the baby is not in bad failure or anything else has happened, the standard peak is at about an hour. Now, recognizing that during that hour, because it is not going in acutely intravenously, we also have a great deal of distribution going on during that time, that is why the peaks in part are not as high, so that we no longer have a simple alpha phase. If absorption is going on gradually, some of the drug now is distributing during that hour as well as contributing to the blood level peak; do you see what I am saying?

Q. All right, you have got a different curve?

A. You have a very different curve and absorption now is a long time, and during that long time some of the drug absorbed is actually going



1
2 to be distributed, so that we cannot talk about
3 simple types of alpha curves, which is at least
4 one reason that, again, I worry about a reading
5 of greater than ten. Had it been achieved orally,
6 a lot of that drug would already have been
7 distributed and again I find it difficult to put
8 together with the baby's clinical ---

9 Q. Otherwise toxicity would have
10 occurred much sooner?

11 A. I would guess. Again ---

12 Q. Well, we do not want you to
13 guess here. That is your best medical opinion?

14 A. My best opinion is yes, and
15 of course we have to accept, again, broad constraints
16 on that.

17 Q. Well, let us see if we could
18 answer the hypothetical I posed to you.

19 A. Yes.

20 Q. Assume that there is oral distribu-
21 tion here, what is the maximum outer time parameter
22 that can be drawn with respect to administration on
23 that hypothetical, can you?

24 A. Not easily, again, because
25 we do not know what -- the problem is we are looking
at one point on an isolated time curve. Is that the



1
2 peak? Is it an hour on either side of the peak?
3 I honestly cannot say. I mean, I share your frustra-
4 tion with it. It is our frustration, too.

5 The problem is that because of all the
6 variables, it becomes very difficult to try to
7 say anything in the absence -- we are trying to
8 solve basically an equation with three unknowns
9 with one known and you just cannot do it. You can
10 put in all kinds of different numbers and get all
11 kinds of different answers out.

12 Q. Is there any way of ruling
13 out whether or not, assuming oral administration,
14 this was on the way down?

15 A. I cannot. Again, if we do not
16 know where the peak occurred, then we cannot really
17 say anything about where the trough would be or
18 where the final -- let us put it this way: if
19 we do not know where the peak is, then we do not
20 know at what time distribution -- when witnesses
21 get tired they have trouble with English.

22 Q. It is still morning, Doctor.

23 A. It is four days for me. If
24 you do not know when the peak occurred and, there-
25 fore, you do not know when absorption from the gut
is more or less complete, then I cannot possibly



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get any kind of idea where the greater than ten
would fit on that peak. I think it is physiologically
unlikely, again, for the reasons we discussed, but
kinetically I think I would be foolish
to try to guess, and it would be a guess.



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Q. It is unlikely that this was on the way down from a higher level because you would have expected toxicity to occur at or about that level, would you not?

A. I would have expected toxicity in a general sense at levels considerably less than that.

Q. So can we assume that in fact, in all probability this child, the curve of this child assuming my hypothetical is on the way up, isn't that the most likely situation, Doctor, given that hypothetical?

A. I really have to sit down and try it mathematically, it sounds superficially reasonable.

Q. I take that as a compliment.

A. But nonetheless I really don't want to try to put constraints on it because I don't think we can.

Q. All right.

A. I don't think we can.

Q. All right, then let's assume, let's take my hypothetical one step further and assume for the purposes of my hypothetical that in fact it is still on the way up, can you now --



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THE COMMISSIONER: Assuming it is oral?

MR. OLAH: Q. Assuming it is oral,
can you now --

A. Assuming it is oral and it is
on the way up, and assuming this baby handles it like
an average baby in the population, we are talking about
a rise over the course of one to three hours.

Q. All right.

A. At most around one, but again
it can vary depending on the illness and everything
else.

Q. And of course this baby probably
wouldn't be like your average baby because of his pre-
existing condition, correct?

A. That is probably true, but again
he really wasn't in congestive heart failure, which is
one - although - well, we can't even say that because
he was getting worse, so we are guessing again.

Q. Probably that time parameter
would be even narrower than the one for the average
baby, would it not? You can't say?

A. Again I can't say.

Q. Fair enough. One more question
if you will indulge me, Doctor. That is, if it is on
the downside of the alpha phase can you put any



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numbers on that, on that phase?

A. No, again I can't because I would have to know when the peak was, and I would have to know whether absorption was complete and there are too many variables. I could literally construct you a whole series of curves, and I would like to be able to and I really can't.

Q. I have been asked to ask you a question now. Apparently yesterday you mentioned something about studies on Dilantin and other literature?

A. Yes.

Q. Can you assist us in that regard at all, is there something you could supply to us?

A. Certainly, yes.

Q. Would you be kind enough to do that?

A. Yes, certainly, I have most of the relevant papers here with me today, some are not here, but I can provide the Commission with that, yes.

Q. I would like to move, and I know Mr. Commissioner you have got your stopwatch on me.

THE COMMISSIONER: It is not me, it is



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Mr. Olah who wants it, and if he wants it you can provide it to him if you will. I have enough things to read without asking for any more, but if you think it is of --

MR. OLAH: Other Counsel wants it, other Counsel wants it and I --

THE COMMISSIONER: If Counsel tender it I will accept it but I am not going to go seeking it.

MR. OLAH: No, I understand that, we would like to see it to see if there is anything helpful to you and that is as far as my request goes.

THE WITNESS: Certainly I have that available.

MR. OLAH: Q. Thank you. Doctor, I would like to, and I am bearing in mind the stopwatch you have on me Mr. Commissioner and I will be just a couple of minutes.

THE COMMISSIONER: It has run out at the moment, it is now almost double what you said.

MR. OLAH: I apologize and I will try to be very brief.

THE COMMISSIONER: Yes, all right.

MR. OLAH: Q. Doctor, in the Cook baby, if we turn to Exhibit 95A, page 3, have you got



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it there?

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A. No.

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Q. Let me tell you what I am

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curious about and see if you can assist us about it.

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There are a couple of samples; for instance, the top

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sample there is "gastric contents", and there is 34

8

nanograms per millilitre fluid.

9

A. Yes.

10

Q. The fluid was found to contain

34 nanograms per millilitre of digoxin; and similarly --

11

A. Which page are you on, I have

been handed this?

12

Q. The top of page 3, Doctor.

13

A. Thank you.

14

Q. The very first sample.

15

A. Yes.

16

Q. "Gastric contents", and

17

digoxin was found in that.

18

A. Yes.

19

Q. And if you drop down a little

further there is bowel contents about the third sample

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down.

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A. Yes.

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Q. Sample of "thick fluid material

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labelled small bowel content", you see digoxin --

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A. The label says "part of small bowel content", yes.

Q. I am just wondering what significance, if any, do you attach to digoxin being found in a child that was not on digoxin therapy, having digoxin found in the gastric component and also in the small bowel?

A. Yes.

Q. Is there anything, a clue there that would assist us?

A. We had initially hoped that it might. The problem is that a fair amount of digoxin is excreted by the liver directly into bile.

A fair amount of digoxin is excreted by the liver into bile. Now what happens is that the bile ducts enter the duodenum or part of the small bowel just beyond the stomach, if you will. The concentrations of digoxin that you can find in bile, even if a dose has not been administered orally, if it has been administered intravenously, can be quite high. The total amount is low, you know, we are dealing with I gather when both Dr. Hastreiter struggled with this and Mr. Cimbura as well as we have subsequently, that the total amounts of digoxin are really extremely small, we are dealing with 600



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2 nanograms which is a fraction of a microgram. We
3 can't therefore interpret whether that digoxin came
4 via bile or via an oral dose. The probability is,
5 given the amounts and the little that is known about
6 biliary excretion, is that it would be very reasonable
7 that that amount would be coming from circulation,
8 going through the liver, and then being excreted into
9 bile.

10 Q. All right, that is where I want
11 to pick up. If you assume that, wouldn't that give you
12 some handle as to when the digoxin administration could
13 have occurred?

14 A. No --

15 Q. Just bear with me for a moment.

16 A. Sure.

17 Q. If it is administered just prior
18 to cardiac arrest, within minutes or seconds before
19 cardiac arrest, wouldn't it take some time for the
20 digoxin to go from the blood, to the heart, to be
21 pumped out into the liver and then to be excreted
22 from the liver in the manner you described into the
23 gastric contents, doesn't it take some time for that
24 phenomena to occur?

25 A. Yes. In fact because the baby
already has tissue levels we can't postulate that it



1
2 was given seconds before cardiac arrest. The fact
3 there were contents present in heart and lung suggests
4 that some distribution did have to occur, as we
5 indicated yesterday.

6 Q. All right.

7 A. So that the fact, in fact what
8 would have been as you say delivered to the liver and
9 that the liver would have excreted some into bile is
10 not at all surprising given all the other data in the
11 child, including the blood levels and the tissue
12 levels.

13 THE COMMISSIONER: A fundamental
14 question.

15 THE WITNESS: Yes?

16 THE COMMISSIONER: Does it have to go
17 to the heart before it can go to the liver, it can't
18 go from the bloodstream to the liver?

19 THE WITNESS: The only way it can go
20 directly, bypassing the heart initially --

21 THE COMMISSIONER: Yes?

22 THE WITNESS: -- is with an oral dose,
23 because part of an oral dose absorbed into what we
24 call the splanchnic circulation, intravenous it would
25 go initially into the heart and then to the lung then
back to the heart and then to the liver.



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MR. OLAH: Q. And can you give us,
does that assist you at all in sort of giving a tighter
rein as to when the administration may have occurred?

A. There are so many variables
that time becomes overwhelmed in that regard.

Q. One final question before I sit
down. The pharmacy, did it keep some sort of an
inventory of dispensation of digoxin to the floor, do
you know about that, was there some inventory kept?

A. There is now.

Q. Do you know if in 1981 there
would have been some inventory kept as digoxin was
delivered to the floor?

A. I honestly don't know, I
honestly don't know, you would have to ask somebody
who was acting in the pharmacy at that time.

MR. OLAH: Thank you Doctor, I am
grateful to you.

THE COMMISSIONER: We will take 20
minutes.

--- Short recess

- - - - -



1 ---On resuming.

2 THE COMMISSIONER: Yes, Mr. Labow.

3 MR. LABOW: Thank you, Mr.

4 Commissioner.

5 CROSS-EXAMINATION BY MR. LABOW:

6 Q. Doctor, you are the first
7 clinical pharmacologist we have seen and I would
8 like to ask you a few general questions about digoxin
9 before I get into the specifics.

10 A. Sure.

11 Q. My name is Stephen Labow
12 and we represent the parents of a number of the
13 deceased children, including Kristin Inwood's
14 parents.

15 A. Yes.

16 Q. Now, Doctor, we have
17 asked similar questions of a number of the doctors
18 and I will tell you what their answers were. We
19 have asked them if digoxin is a dangerous drug to
20 use in that it has severe toxic effects if an over-
21 dose is given of some kind. Do you agree with that?

22 A. Certainly.

23 Q. And that the toxic effect
24 is more likely to occur if the heart is damaged in
25 some way?

A. Yes.

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Q. We have also asked them
if for those reasons the patients should be monitored
very carefully because it would be important to note
and to estimate the degree of improvement in the
circulation after digoxin is administered?

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A. Yes.

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Q. And that clinical

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observation is the best way to monitor the effects
of digoxin?

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A. Certainly if we are

11

dealing, you know, for example with issues of
efficacy, how well the drug is working, our clinical
observations, echocardiography and such can help us.
But typically one uses what one would call I suppose
astute clinical observation as probably the best
guide to therapy, yes.

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Q. Now, you have pointed out
to us that the best diagnostic tool that you would
have as a clinician would be to stop the drug if
there was some suspicion and then observe the patient?

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A. Suspicion of toxicity?

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Q. Suspicion of toxicity.

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A. This would certainly be

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helpful in that again we said that the various
different signs and manifestations of toxicity are

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2 indeed the same as many of the diseases which we
3 are treating. So that if we wish to try to separate
4 the effect of the disease from the effect of the
5 drug, dechallenge or decreasing the amount of drug
6 in the patient is a helpful tool, yes.

3
6 Q. Now, we posed a hypothetical
7 question to most of the doctors who have testified
8 to date and it is that you were observing a patient
9 with a heart problem, and this can be found in
10 Volume 24 at page 4349 for Dr. Rowe, and the patient
11 is being given digoxin and diuretics. Now, this is
12 an infant, you know nothing more about the patient.

12 A. Do we know which diuretic?

13 Q. No. Lasix, for example.

14 A. Okay, because most of
15 the patients are on aldactazide.

16 Q. Okay.

17 A. Because that does make a
18 difference in interpretation.

18 Q If you observed the
19 patient vomiting and confused on awakening and
20 showing symptoms such as giddiness, what would your
21 first diagnosis be?

22 A. I'm not sure what giddiness
23 is in an infant, nor am I sure what confusion is. I
24
25



1
2 think we would have to be a bit more specific in
3 terms of what the child was doing and what the nature
4 of the vomiting is. I mean, I can't tell from that
5 description. I mean, that is one description in an
6 adult, a confused, giddy adult who is vomiting.

4 6 Q. Right.

7 A. Is this an infant who awakes
8 from sleep and spits up a little bit or is this an
9 infant who is retching. I can't really answer, I
10 would have to examine the patient, look at the patient,
11 see the last time he or she was fed, how well the
12 baby tolerated the last feed, then I would have to
13 look, for example, if there is any evidence of
14 increasing failure, heart failure, I would examine
15 the baby's liver, I would examine the baby's heart
16 rate, respiratory rate, listen to his or her lungs
17 and from that then try to make an assessment whether,
18 for example, worsening heart failure might be playing
19 a rôle in the symptoms I am seeing or whether it was
20 a feeding problem, whether the baby had developed
21 a temperature, whether the baby's temperature had
22 come down below normal; all the parameters that you
23 would use in looking at an infant and then make a
24 reasonable assessment based on everything we have
25 known clinically up to that point, is this a new



1
2 sudden change, is this a gradual change, is it part
3 of the child's disease, do we have evidence for
4 something else going on and then perhaps I do a
5 series of laboratory tests, potassium, for example,
6 a blood count if the child was febrile or looked
7 septic because leading the list in lung children,
8 presenting for example with vomiting in a clinical
9 setting on a cardiology ward, you would be concerned
10 about (1) very high on the list would obviously be
11 the child's disease process per se and (2) you have
12 to be very concerned about sepsis, infection in that
13 little infant particularly, number one, have decreased
14 immune defences against infection, (2) are likely
15 to get infections with heart disease because of the
16 abnormalities in their hearts and (3) it is very
17 difficult to diagnose. That's why you might notice
18 on many charts babies will be begun very rapidly
19 on antibiotics even though you haven't made the
20 final diagnosis because of the risk of infection
21 and the overwhelming nature of infection in very
22 little infants particularly.

23 Q. Well, Doctor, if you are
24 faced with a child who shows a continuing propensity
25 to vomit.

A. Yes.



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Q. Is on digoxin and diuretics.

3

A. Yes.

4

Q. You know the child has some
kind of congenital heart disease.

5

A. Yes.

6

Q. Whatever kind that is.

7

A. Surely.

8

Q. Would you want to rule
out digoxin toxicity as a possible cause?

10

A. Yes.

11

Q. By taking a level, for
example.

12

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A. I think you would, first,
before taking a level you would examine all the
other parameters which might help you in that regard.
An EKG might be helpful. Again, I am not really
expert enough in electrocardiology to help you with
all the specifics of what you would look for. But
there are signs on an EKG which might help, again,
recognizing that the abnormality in the heart may
be such that you can't detect those particular signs.

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You would obviously look at other
manifestations of toxicity, heart rate and the other
arrhythmias, again recognizing that those can overlap,
and you might then also want to look at a digoxin

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2 level.

3 Now, as we have said before, there
4 can be patients with even low therapeutic levels of
5 digoxin whose symptoms are due to digoxin toxicity.
6 So, getting back a low level does not necessarily
7 assure you that it is not digoxin toxicity and you
8 would have to look at potassium and all the other
things that we talked about.

7 9 Q. Can I stop you there for
10 one moment?

11 A. Surely.

12 Q. We have asked the doctors
13 whether a low concentration of digoxin, a level
14 that gave you a low concentration in the plasma would
15 preclude the possibility of toxicity and I don't
16 think I received a very clear answer. Now, I do
17 know from reading Goodman and Gilman, which you
referred to.

18 A. Yes.

19 Q. At page 751 and 2 that
20 they point out that low concentrations do not
preclude the possibility of digoxin toxicity.

21 A. That's correct.

22 Q. How low a concentration
23 are we talking here. I mean, exceptionally low?

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25



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2 A. I think we can't even
3 say, again, because it is so variable and because
4 the correlation between level and the amount in the
5 myocardium is variable all over the map and because
6 of all the other clinical variables.

7 Certainly we can say, however,
8 that - and again referring to Goodman and Gilman as
9 an example of a statement that is clearer than I
10 could make -- now I have forgotten the statement.
11 Where were we? I'm terribly sorry.

12 THE COMMISSIONER: Talking about
13 whether low readings ---

14 MR. LABOW: Low concentrations.

15 A. Oh, okay. That basically
16 if you think about digoxin toxicity the most likely
17 cause that comes to mind is excessive administration.
18 The most frequent cause of digoxin toxicity, however,
19 is hypokalemia or a low potassium level with a
20 therapeutic digoxin level. That is certainly true
21 in adults. Children in general aren't quite as
22 likely to get into the potassium related hypokalemia
23 problems and many of the children at the Hospital
24 for Sick Children on the Cardiac Wards are treated
25 with aldactazide, one component of which tends to
help the body retain potassium and prevent it from



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being lost in the kidney.

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But, yes, you can have therapeutic levels of digoxin and have clinical toxicity from the drug. How low that could go I think would be dependent on the patient's status and all the multiple variables which we alluded to earlier on.

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Q. Now, Goodman and Gilman

point out that not only a larger than therapeutic dose or a mistaken dose could cause toxicity but an improved absorbtion of the drug due to physical changes could also lead to toxicity?

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A. Yes, this is what we had

discussed before. For example, the patient on oral therapy who might initially be in heart failure, what happens is that the profusion of the gut in the absorbtive surface is decreased, as such absorbtion isn't as efficient. As the patient improves, assuming the same dose be given, then the possibility exists of more absorbtion and a higher level achieved from the same dose.

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Q. Now, Doctor, I would like

to refer to Exhibit 217-1. That was your first graph.

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A. Yes.

Q. Discussing the kinetics



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of digoxin?

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A. Yes.

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Q. Is the distribution to

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the tissues after the acute phase?

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A. Yes.

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Q. An ongoing process until
you reach steady state?

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A. This is our general notion.

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It is based of course on measurement of blood levels
over time and the relative rates of disappearance of
drug from blood into tissues. The only kind of
experiments where you can do that, comparing
simultaneous tissue in blood of course is in animal
models and the concept has been accrued both from
information in animals as well as information in
humans, for instance, intra-operative patients or
situations where we can readily measure blood
repeatedly in an experimental sense.

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Our general concept is that that
alpha phase with a range of 20 to 26 minutes perhaps
under normal circumstances represents tissue -
excuse me, digoxin leaving the central volume of
distribution into the rest of the body.

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Q. Now, does it proceed as

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far as you know exponentially; in other words, in

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2 the first half life of the five half lives is one-
3 fifth of the digoxin transmitted to the tissue or
4 not like that at all?

11 5 THE COMMISSIONER: No, that why
6 it is called a half life because half of it goes,
7 isn't that right?

8 THE WITNESS: Yes, exactly. It's
9 as an exponential half life function. So that, for
10 instance, let's say we are at 20.

11 Q. Yes.

12 A. In one half life it goes
13 from 20 to 10, the next half life from 10 to 5, the
14 next half life from 5 to 2.5, the half life remaining
15 more or less constant during that period of time.
16 That is at least our assumption.

17 THE COMMISSIONER: We never have
18 a full life either. We can't.

19 THE WITNESS: We usually talk
20 about completion as five half lives since in an
21 exponential curve five half lives represent somewhere
22 above 95 per cent of distribution. So, for practical
23 purposes we are talking about completion at that
24 point.

25 MR. LABOW: Q. Now, if you assume
that there is some kind of impairment of the



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(Labow)

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circulatory system.

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A. Yes.

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Q. Is the alpha phase extended?

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A. We do not have good data on that. Again, that is something that will be helpful to us, and one of the quandaries that we have, for example, what effect disease process per se can have on distribution.

All we do know from studies in different infants with different diseases is that in fact it can be highly variable. We gave an average, say, of 30 minutes, but certainly much shorter and much longer can occur in any individual patient.

The basic notion that I hope we have been able to bring out in general about all these kinetic parameters is that there is a wide range of inter-individual variability, as we see with all compounds. To say, you know, a specific disease process alters it in a specific way we do not have those data available.

Q. Now, turning to your discussion of pathophysiology, and that being a reason for the levels rising, did you eliminate the possibility that these children were administered digoxin by error or intentionally prior to taking your readings that showed a rising level?

A. For them -- on the children --

Q. On the three that you --

A. Subsequent children. We made



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basically, for example, in the case of Gary Murphy which was the most thoroughly investigated and which was already been documented, every attempt to look for possible means and mechanisms and modes of administration. I think these were discussed more eloquently by Dr. Kauffman than I can provide at this time because I do not really have, you know, all of the various considerations in front of me.

The basic issues under those circumstances are that the baby did not have an intravenous line in place, that there was no evidence of oral administration after looking at gastric contents, they looked at the endotracheal tubes and sometimes drugs can actually be given via the endotracheal tube, looking at every possible route, possible explanations, possible modes, reviewing the chart, reviewing the history, trying to put all that together, and again, I do not remember every parameter that had been examined but a whole series had been, we were left with the very high probability in fact that the child had not received excessive digoxin and that therefore we had to look elsewhere for such a phenomenon as we saw in this child.

Similarly with the other children that we see clinically on the wards, we again try as best



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as possible to go back through the patient's records, talk with the nursing staff, talk with the medical staff and try to ascertain whether there was a possibility, for example, of an error being made or of administration being made. Again, we feel reasonably confident that in the cases that we have been involved in that in fact we are dealing with a phenomenon such as we have discussed, and the literature tends to confirm this now.

Q. Now, I would like to refer very briefly to child number C in your example.

A. Yes.

Q. That was the child with the severe skin disease?

A. This was the skin disease where the digoxin level --

Q. And five days later the level was the same?

A. -- help up basically at the same level, yes.

Q. Now, did you know as well as you can or could have at the time that the 4.4 reading was the steady state reading?

A. We believe that it was in that the numbers had actually increased from the previous



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day, no administration had occurred, and that number then remained, if you will, steady.

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Q. Now, your evidence with regard to Exhibit 217 was that the beta phase is much slower, the half lives are 20 to 80 hours?

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A. Much, much slower, yes.

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Q. Could it be more than 80 hours?

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A. Yes.

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Q. So it is conceivable that with this child the half life of the drug was more than 80 hours and there was no perceptible difference?

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A. It is conceivable. The things

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that mitigate against it in that particular case were the normal renal function, the normal creatinine,

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normal urine output. There is obviously a great deal of variability. Eighty hours is how many days? I

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suppose we are talking in the neighbourhood of a little

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under -- three days under which circumstances we would

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have expected it to come down to at least 2.2. The

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fact that it did not change at all is quite striking,

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and here we are getting at least well beyond any

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numbers that we have seen in the past.

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Again, perhaps the reason that this was

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holding up was because this child had some sort of

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funny excretory problem in his renal tubule, which

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again is another, if you will, pathophysiologic explanation of why the level did not come down. I do not pretend to fully understand that in this child. The point is that we observed it.

Q. My only other question dealing with that is what kind of assay procedure were you using, the standard RIA that the hospital uses?

A. For these assays, I forget the name of the machine that is presently being used. It is a fluorescent polarization assay which is an antibody based assay.

Q. Now, I would like to turn to Kristin Inwood. Now, Doctor, you know that in Kristin Inwood's case digoxin was ordered held after she had been admitted?

A. Yes.

Q. And she was to receive no digoxin but did receive a dose in error?

A. Yes, that was, I believe -- well, I do not have the exact timing, but that is my understanding.

Q. On the 12th of March at 5:30 in the morning?

A. Yes.

Q. Now, we know from our statement



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of facts that the EKG on her admission showed signs of digoxin toxicity and that is why digoxin was held. Now, she received a dose of digoxin, a large dose --

A. Yes.

Q. -- at 5:30 in the morning on the 12th?

A. Yes.

Q. But the level at 9 o'clock in the morning was only 2.6?

A. Yes.

Q. Now, would you plot that on your graph in the alpha phase going down the steady state or at steady state?

A. This was an oral dose, I believe.

Q. This was an oral dose.

A. It is going to be very hard to plot. Do we actually -- I do not have in my notes the actual amount that she did receive.

Q. We do not know from the incident report or from the hospital record, that I know of.

A. Okay, because I do not have it in my notes.

THE COMMISSIONER: Does it not say the amount?

MR. LABOW: No.



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MR. BROWN: Excuse me, Mr. Commissioner,
I understand that the dose that she received was the
dose that was intended for Kevin Pacsai.

MR. LABOW: I thought it was for
Manojlovich.

MR. BROWN: So if we know his dose --

THE WITNESS: I am sorry, I do not have
that available immediately.

MR. LABOW: Q. Well, assuming that
you are --

A. That obviously is important.
Without the dose we cannot really do much.

MR. BROWN: If I could be of further
assistance, I think the dose was 0.02 milligrams.

THE WITNESS: About 20 micrograms, okay.

MR. LABOW: Q. If we know that that
was received orally at about 5:30 and you have told
us that approximately one to three hours to peak with
an oral dose --

A. Right.

Q. -- then we can assume it was
past the peak at the very least and on its way down
the alpha phase?

A. Well, let us not use alpha
phase for oral administration because again we have



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distribution going on during absorption, so we have a very different kind of pharmacologic process going on. So we are talking about, then, the baby receiving a dose -- the other thing we do not know is her prior level.

Q. Because she had just been transferred to the hospital?

A. Yes, so that we are sort of adding guesses upon guesses upon guesses. I will try to do the best I can with it.

Assuming it was 20 micrograms, that would be about 10 micrograms per kilograms -- well, a little less than 10 micrograms per kilogram. I believe her weight at admission was 2.6 kilos; is that correct?

Q. I think that is correct.

A. I do not have the chart here. These are just my notes. So she was about 2.6 kilograms. Does anybody have a calculator? Could I borrow one just for a second because rather than trying crude guesses, let us at least calculate it through so I can give you some numbers.

All right, so we are talking about 20 micrograms in a 2.6 kilogram infant. So we are talking about --



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Q. Exhibit 113 the medical record,
it should be right beside you.

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A. Thank you. I am not sure that
will help at this stage. I assume those doses are more
or less correct?

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Q. Yes.

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A. Then we are assuming somewhere
in the neighbourhood of about $7\frac{1}{2}$ micrograms per kilo-
gram for that dose. Again, absorption is going to be
highly variable. We are not going to be able to give
you a clear-cut estimate and we will have to go back
to other absorption studies. The data I presented to
you yesterday in terms of absorption was for 10 micro-
grams per kilogram given to a series of infants about
Kristin's size, different diseases, of course, and
they ended up having peaks in the neighbourhood of
about 5 micrograms -- excuse me, 5 nanograms per ml
plus or minus 1 or 2 nanograms per ml at about an hour
or so after administration, and then a gradual decrease
after that period of time which is a combination then
of distribution of the drug, the beta phase elimination
of the drug, and perhaps some continued absorption if
absorption is still going on.

So we might expect under these circum-
stances peaks that would be under 5 nanograms per ml,



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since this child received about $7\frac{1}{2}$ micrograms per
kilogram, and the babies that we have data on received
about 10 micrograms, and then a level of 2.6 not at
all uncomfortable or unreasonable within those broad
limits.

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Q. She died approximately 21-1/2 hours after that dose?

A. Yes.

Q. So at the very least -- and she received no other digoxin that we know of.

A. Yes.

Q. That was prescribed.

A. That is correct.

Q. At the very least we can assume that the digoxin in her system was being eliminated, there may have been some but it would have been in the elimination phase.

A. Yes. To give you a little bit better -- I don't know what her BUN was towards the end, what her renal function was like. I believe it was more or less all right. Let me see if we have any data on that, because that might help give us at least -- if it was grossly abnormal then her half-life of elimination would be somewhat longer. On March 11th her BUN was 15, elevated, but not tremendously abnormal.

Certainly with a BUN in that range we would expect some excretion of that -- some excretion of the digoxin over that time, so that we would expect that 21 hours later that level would



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2 be less than 2.6. How much less, I think again we
3 are speculating. If half-life was 24 hours it
4 would have been down to 1.3; if her half life was
5 48 hours it would have been down by one-quarter.
6 So, it might have been down to, say, 2.0, but
7 again (very, very roughly.

8 Q. Now, we also have for
9 Kristin Inwood, and that is in Mr. Cimbura's January
10 11th report, a sample and it was sample No. T-26.

11 A. I don't have that.

12 Q. Of yellowish fluid, that is
13 Exhibit 95-A; the first report, and it is Page 7.

14 A. Yes.

15 Q. A sample of yellowish fluid,
16 that of blood, that was apparantly taken antemortem
17 when Mr. Cimbura could find no digoxin, with a detection
18 limit of two nanograms per ml.

19 A. Yes. Am I correct that that
20 was the same sample that we have 2.6 on, or was
21 that a different sample?

22 Q. My understanding is it was a
23 different sample from hematology, from Dr. Kuhn, a
24 vial of blood.

25 THE COMMISSIONER: What number is
this?



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MR. LABOW: T-26.

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THE COMMISSIONER: The T-26 and the

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page?

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MR. LABOW: Page 7.

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THE WITNESS: Page 8.

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MR. LABOW: Page 8, I'm sorry, of the
first report, Mr. Commissioner.

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THE WITNESS: Now again in order to
interpret that I would have to know what the rela-
tive timing of that sample was versus the other
sample.

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Q. Okay. Now, without getting
into drastic interpretation.

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A. Yes.

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Q. We know that at the very most
he had some with under 2 nanograms in her blood,
2 nanograms per ml. of digoxin before she died.

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A. If that detection limit is
correct.

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Q. The detection limit, according--
excuse me?

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A. My only concern was, for example,
if it was taken basically the same time and one
laboratory gets 2.6 and another laboratory gets
less than 2, that is probably due to a difference in



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2 assay techniques, and I can't say less than 2, in
3 fact, it could have been 2.6, but within those
4 constraints, in any case. So I am not sure that
5 that has a great deal of additional information to us
6 at this time.

7 Q. Then, Doctor, we have the 491
8 nanogram level.

9 A. Yes.

10 Q. Now, your reservations, from what
11 I can understand, were first that you were not sure
12 it was serum, but I think that has been cleared up
13 somewhat, that it was serum from Virology.

14 A. Yes, prepared in exactly what
15 manner we are still, you know, we can't really be
16 100% sure.

17 Q. And then you had a question about
18 where the sample was from?

19 A. Yes.

20 Q. And we don't know for sure but
21 Dr. Taylor indicates that he usually takes the blood
22 from the inferior vena cava.

23 A. Yes.

24 Q. Now, you are assuming that
25 this sample, your best guess, is that this sample
was probably taken in the pre-alpha phase, the acute



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1

2

stage.

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A. If it represents a real number.

4

Q. Yes, if it represents a real

5

number.

6

A. Yes. If it represents a real

7

number, I think the most reasonable explanation
would be such an alpha phase distribution, yes.

8

Q. Or if a blood sample is taken

9

at that time in the acute phase, is there any

10

distribution to the tissues?

11

A. Again, we will be talking in

12

terms of how rapidly, okay? That, again, we can't

13

really know for sure; as we indicated, circulation
ceased very quickly; there may be little distribu-

14

tion. If circulation continued for a brief period

15

afterwards, there might be some distribution.

16

Again, one of the problems we are dealing with is,

17

even if we are invoking even accidental or intentional

18

administration of an amount of digoxin to produce

19

even that kind of level and peak, we are still talk-

20

ing about huge amounts of digoxin relative to a

21

normal dose.

22

THE COMMISSIONER: Doctor, doesn't there

23

have to be some distribution if the death is going to

24

result from the digoxin?

25

25



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THE WITNESS: If the death results from
the digoxin.

3

4

THE COMMISSIONER: Yes.

5

6

7

THE WITNESS: If the death results
from something else, for example, propylene glycol
as an example, and I don't mean that as an exclusive
example.

8

9

THE COMMISSIONER: No.

10

11

12

THE WITNESS: Then death might occur
much more rapidly and the digoxin hasn't had a chance
to distribute, but the digoxin nonetheless is
present in that sample and at very high concentrations.

13

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So to answer your question as best I
can, we could be in a situation where reasonably
little distribution has occurred; and we might be in
a situation where a reasonable amount of distribution
has occurred, but probably not very much because we
are again talking concentrations, again, if we are
invoking a single vial, we are talking about very,
very short time intervals. If we are again talking
about multiple, multiple, multiple vials and down
to steady state then we are talking about a very
different scenario.

22

Q. Of course.

23

24

25

THE COMMISSIONER: Are any vials



1
2 available anywhere, that you know of, that are
3 greater than the adult concentration vials?

4 THE WITNESS: Not that I am aware of,
5 sir.

6 THE COMMISSIONER: They are not put out
7 by anybody?

8 THE WITNESS: I don't believe so, no.
9 I think that is the maximum size. Again, because
10 one would rarely, if ever, want to use more than
11 that, even in a very large adult than a single
dose.

12 Q. You have not made mention really
13 of any of the fixed tissue results.

14 A. That is correct.

15 Q. That Mr. Cimbura found, not
16 because you don't think you can conclude much from
them.

17 A. Yes.

18 Q. But in Kristin Inwood's case
19 they did find relatively high levels of digoxin in
20 her heart.

21 A. Reasonable concentrations,
22 yes.

23 Q. Are they reasonable concentra-
24 tions, that was my question.
25



1
2 A. They are -- again, we are
3 talking about now levels that we find in living
4 patients anywhere from a few nanograms per
5 gram up to 800 nanograms per gram under therapeutic
6 circumstances. So it certainly is well within the
7 range of therapeutic digoxin concentrations.

8 The problem is, and the thing I suppose
9 that we have again all struggled with, including
10 Mr. Cimbura, and very hard, is trying to assess what
11 effects preservatives have on that level. In other
12 words, might we expect that that level would be
13 much higher, or nor much higher, in life, and un-
14 fortunately all I can say is, we don't know.

15 Q. Mr.Cimbura concluded that
16 he estimated the concentration of digoxin in the
17 heart before it was fixed at not less than 549
18 nanograms per gram.

19 A. I would be very cautious in
20 those interpretations, extremely so.
21 Because again we are not quite sure what we are
22 always measuring. We are making guesstimates of
23 fluid volumes surrounding the heart, and trying to
24 extrapolate that back to what was in tissue. I
25 would be a bit more cautious than he was on that.
I think there are so many variables that to assign



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a number under those circumstances is hazardous.

3

If it is 500 it still doesn't help me, really,

4

because that is still well within the therapeutic

5

range and we know that the child had a reasonable

6

digoxin concentration, in fact, a high therapeutic

7

digoxin concentration only 21 hours prior to death;

8

and even if her half-life was 40 hours, most of that

9

digoxin would still be in tissues.

10

Q. That was my next question.

11

A. Yes.

12

Q. So the fact that she previously

13

had digoxin administered, that the one that she

14

received mistakenly could account for both levels

15

in her tissue.

16

A. I think so, sure.

17

Q. Aside from the fact that you

18

don't put much credence into the tissue levels, if

19

digoxin is found in tissue, is my understanding

20

correct that you feel, as of your present knowledge,

21

that they must have received some digoxin at some

22

time.

23

A. If we have a combination of

24

RIA, HPLC, and mass spectrometry confirmation of

25

the presence of some digoxin in tissue. Again,

barring the caveat of whatever this other substance



1
2 is going to be, and whether it is going to cross-
3 react across the board, which it might, barring
4 that, one must for the moment accept administration
5 as the most likely explanation of the presence
6 of that drug, yes.

7 Q. Now, aside from our caveat,
8 are you saying that if we only have RIA, HPLC and
9 then RIA again, that you wouldn't be even as
10 unsure as you are now.

11 A. Our confidence does go down a
12 bit. Again, because it appears some of these cross-
13 reacting substances do travel in the same relative
14 position on a high pressure liquid chromatogram
15 column, and again I am not an analytical chemist,
16 that question has to be left to the analytical
17 chemist. But my level of understanding of that
18 is that with what we know now, there can be
19 cross-reacting substances that will react with
20 the RIA that travels in the same position as the
21 HPLC, so we may not be able to separate that from
22 digoxin as such.

23 Q. Using the same type of con-
24 clusion as we just used, at your level of knowledge
25 today, if we find digoxin in tissues of children
after RIA, HPLC, RIA, would you today conclude that



1
2 that is probably digoxin and that it was administered
3 at some time?

4 A. I still in a broad sense have
5 to conclude my confidence is less than if we had further
6 information. For example, mass spectrometry. How
7 much my confidence goes down is again going to be
8 dependent on the information coming forth over the
9 next how ever many months to years. I must keep
10 that as a reservation because that field is
advancing at an extremely rapid rate right now.

11 Q. I understand the reservation,
12 but today what is your conclusion?

13 A. Today with the data we have
14 I would have to accept administration as the most
15 likely, but with other possibilities existing.

16 MR. LABOW: Thank you.

17 I have no other questions.

18 THE COMMISSIONER: Thank you.

19 MR. SHINEHOFT: Mr. Commissioner, Mr.
20 Tobias has asked me if I might replace him in the
order of cross-examination.

21 THE COMMISSIONER: Yes, all right.
22 What does Mr. Shanahan say about that?

23 MR. SHANAHAN: No problem, sir.

24 THE COMMISSIONER: All right.
25



CROSS-EXAMINATION BY MR. SHINEHOFT:

Q. Doctor, my name is Jack Shinehoft and I represent the parents of Kevin Pacsai. Do you have his chart present, Doctor?

A. No, I don't.

Q. I might be referring to it, sir, so perhaps you should have it.

A. Sure.

Q. Do you have it now?

A. No, not here.

Q. It is Exhibit 106, Mr. Registrar.

A. Thank you.

Q. Doctor, you said in your evidence that you found Kevin the most complicated of all the children and you went further on to state:

"We are unhappy with that fact as well because we do not understand a great deal about him."

Does that correctly paraphrase what you said?

A. I think that is a fair statement, yes.

Q. Perhaps you could start by indicating to me, Doctor, exactly what you are concerned about as far as this child is concerned.

A. There are a number of areas which



1
2 we have already reviewed with respect to both
3 his clinical presentation; some of the laboratory
4 values that we found in the child; and some of the
5 resultant events that subsequently happened.

6 The profundity of his initial presenta-
7 tion, of course, is of concern. This child was,
8 when he arrived at St. Joseph's, if you will,
9 clinically as close to death as anyone can possibly
10 be. Now, that is not an impossible scenario, for
11 example, in a child with a cardiac arrhythmia,
12 profusion is very bad.

13 One of the things that I don't quite
14 understand in fact is that his initial pulse on
15 admission, however, was about 160 which is not all
16 that abnormal. Subsequently he had a tachy ar-
17 rhythmia or an increased heart rate, but on his
18 arrival the heart rate was reported as 160 with no
19 blood pressure.

20 Q. So that is the first thing
21 you are concerned about was his condition on
22 arrival at St. Joseph's?

23 A. Which was profoundly ill,
24 yes.

25 Q. And I understand as well that
you are concerned about the Ph level of his blood?

A. Yes.



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A. Certainly it is consistent with a baby in shock. Now, we don't have a good feel for exactly how things went at St. Joseph's but we do know that for a period of nearly three hours his blood pH remained below, I think the final pH prior to transfer was 7.07, which is still profoundly acidotic.

Q. Can I just interrupt you there?

A. Sure.

Q. My understanding, Doctor, is that the pH level of blood is derived by a mathematical formula. Is that correct?

A. It's measured.

Q. It's measured by a mathematical formula?

A. No, it is measured by a machine that measures pH. It is the negative log of the hydrogen ion concentration.

Q. You mean you do not use formulas or equations to derive the pH level of blood?

A. No.

Q. So, you don't take for example the pO_2 and the pCO_2 and the bicarbonates and you put them altogether in a formula to come up with --

A. The PO_2 is relevant in terms of pH. Okay, so, we can remove that as an issue. In



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general, depending on the blood gas machine that you have, okay, and I don't know what machine was particularly used there, is that the machine has an electrode which measures pH and there is another electrode which measures pCO₂ with a concentration of carbon dioxide as one of the gases. From that you can then extrapolate an estimate of bicarbonate concentration. Typically the machines do not directly measure bicarbonate. That number is extrapolated on the basis of information related to the partial pressure of carbon dioxide in the solution, the partial pressure above that solution and the measured pH of the blood.

Q. Okay. Now, dealing specifically with the Pacsai child. Did you infact do this second calculation to ascertain whether the figures that were given to you from St. Joseph's Hospital and McMaster University were in fact correct?

A. I did not back recalculate them. They seemed fairly reasonable on the surface.

Q. Well, if I were to tell you that they were incorrect, Doctor, would you disagree with me?

A. I haven't done the calculations, so, I can't disagree.



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Q. Well, can you quickly do the calculations or is that a fairly ...

A. I would need a nomogram. Those are not things that one can calculate with a hand calculator.

Q. I see. Now, the third thing I think that you indicated that you were somewhat concerned about was the fact that this baby when, after going into the ICU, went back to normal sinus rhythm, is that correct?

A. No, there are several other things still.

Q. Okay.

A. We are still back.

Q. All right.

A. The fact that his potassium was very high initially when he was at St. Joseph's is reasonably consistent with acidosis initially. However, we also know that subsequently when he was alkalinized with a bicarbonate that was very high at McMaster, in fact, his potassium remained high normal, 4.5, that range, one might have expected that if all the potassium related problems were due simply to ionic shift, hydrogen ion exchanged for potassium ion across a membrane, that his potassium might have



1
K 4 2 settled down somewhat lower. It is a little bit
3 unusual and it is a little bit worrisome.

4 The third thing was that the child's
5 temperature was extremely low and that his blood
6 glucose was extremely low. The combination of all
7 of these features, particularly during an extremely
8 long period of resuscitation attempts prior to his
9 transfer to McMaster make one worried with respect to
10 the thing that digoxin binds to, the sodium potassium
11 ATPase because that particular binding site is
12 dependent on supplies of sugar, supplies of oxygen,
13 acid can alter that and because of all these features
14 and the profundity and the length of time involved
15 here, which is really quite long, we are concerned
16 with respect to how that might subsequently influence
17 the way in which a membrane, having survived three
18 hours in that condition, would interact with digoxin.

17 Q. Well, do you have any comment,
18 Doctor, on his presentation at the HSC in terms of
19 his medical condition?

20 A. At that time there was continued
21 concern about the child's bradycardia.

22 Q. Well, no, just on presentation.
23 It is my understanding, Doctor, that he was in
24 relative - and we have heard some evidence to that
25



1
K 5 2 effect - that he was in relatively good condition on
3 his arrival.

4 A. No, relatively of course is
5 dependent on who else you are seeing at the time. If
6 I was the physician receiving him, recognizing that he
7 had been essentially clinically dead for nearly three
8 hours only a few days before and that he was
9 transferred to me, because the physicians were still
10 concerned about a persisting bradycardia, even though
11 at that time he was pink and moving and active, I
would be very concerned.

12 Q. But you did not examine this
13 particular baby on his arrival at the Hospital for
Sick Children?

14 A. No, I did not.

15 Q. So, you would have to accept,
16 would you not, the opinions of the clinicians that did
17 examine this baby upon his arrival at the HSC as far
18 as their opinion is concerned in regard to his
19 clinical condition?

20 A. Relative to how I know that I
and other physicians write notes, yes.

21 Q. Well, he was seen by Dr. Fowler?

22 A. Yes.

23 Q. He was seen by Dr. Costigan?
24
25



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A. Yes.

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Q. And I believe the evidence that

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they have given is that he, from a clinical point of

5

view, was in good condition on his arrival at the

6

Hospital for Sick Children?

7

A. At that moment he appeared to

be reasonably stable, yes.

8

Q. Do you have any evidence that

9

would disagree with that opinion?

10

A. No. He appeared, at that time

11

on arrival, despite the obvious concerns of the people

12

at McMaster for, again, if this was simply a child

13

with paroxysmal atrial tachycardia, a simple arrhythmia

14

such as he might have presented with, there would be no

need to transfer him.

15

Q. Well, obviously they were

16

concerned about his electrical conduction problem or,

17

as you say, he would never have been admitted to the

18

HSC in the first place?

19

A. Exactly, exactly.

20

Q. Okay. Now, Doctor, what is your

next concern about this baby?

21

A. Now, he is in hospital, we know

22

already that the arrhythmias which he is experiencing

23

prior to his arrival here end up being very similar to

24

25



1
2 the arrhythmias or disrhythmias, if you will, that he
3 experienced while in the hospital here. His father
4 in fact reported before he arrived at St. Joseph's
5 that in fact there seemed to be an increasing and
6 decreasing heart rate. That was the note from the
7 transfer note initially. I think parents are pretty
8 good observers of their children, we often don't give
9 them adequate credit. So, we have at least some
10 evidence that in fact even prior to the time that he
11 arrived at St. Joseph's that he was having an
12 arrhythmia and he continued to have an arrhythmia in
13 hospital here which ultimately led to the events
14 associated with his transfer from the ward to the
15 intensive care unit.

16 Now, as such, I would not be particularly
17 surprised that what we were seeing while he was in
18 hospital was an extension of his prior arrhythmia
19 which, in the absence of any medical setting, had
20 nearly caused his death a few days before.

21 Q. Or it could have been, Doctor,
22 another explanation it surely could have been from an
23 overdose of digoxin?

24 A. We always have to consider that
25 possibility, yes.

Q. Now, the other problems that



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you are concerned with?

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A. Then we have to deal with his course and timing of the events which subsequently occurred. These are obviously difficult to cope with and I find it difficult therefore to explain some of the phenomena which we saw in the child. He is transferred to the ICU but we know survives in the ICU for a period of hours, not minutes or seconds.

Q. No, but it is not four hours that you had previously indicated?

A. I don't remember the exact time of course.

Q. Well, he is admitted to the ICU at approximately 6:00 a.m. and he arrests at approximately 8:45 a.m. Would you accept those as correct?

A. If that is what the admission records show, surely. So, that is two and three-quarter hours. Now, from a pharmacologic distribution point of view of digoxin as we have said with respect to alpha phase, two and a half hours is a reasonably long time in fact. It is not absolutely the outer limits of distribution but it is a rather long time.

Q. Well, you had previously given evidence I believe to Mr. Labow that this child could



1
2 have very well been in the beta phase of distribution,
3 is that not correct?

4 A. Well, the issue that we have to
5 cope with is pharmacologically and clinically we have
6 two numbers to deal with. We have a number which says
7 greater than 10, which was extrapolated to 10.6. We
8 will assume it is more or less 10 or a little above
and a 26 postmortem.

9 Q. You said that those two numbers
10 are consistent, relatively consistent?

11 A. Those two numbers are
12 reasonably consistent with a large volume of data
13 comparing premortem and postmortem digoxin
concentrations.

14 Q. Yes.

15 A. Recognizing again that there is
16 a big range, that comes very close to the mean. The
17 mean that has been published is about 3.2, this would
18 be about 2.6 fold.

19 Again, recognizing that that is difficult
20 to interpret. The problem that I suppose we have to
21 deal with and that again we have to try to come to some
22 kind of answer, and recognizing that I don't think we
23 fully can, is that during the time in the ICU he
24 obviously survived for a period of time. We are not
25



1
2 talking seconds, we are not talking minutes, we are
3 talking at least two hours, two and a half hours, two
4 hours 45 minutes. During a portion of which at least
5 the child is now back in sinus rhythm. Now, the
6 problem is that whatever was wrong with Kevin with
7 respect to what started his arrhythmia which led to
8 his admission to St. Joseph's, those kinds of rhythm
9 disturbances in a broad sense, and certainly we would
10 highly expect in this child might predispose him to
getting into trouble with digoxin.

11 Q. Well, just on that vein.

12 Dr. Costigan when he gave his evidence, and this is at
13 page 2292, line 4, and I am sorry, I don't have the
14 volume, he makes the differential diagnosis of brady
15 arrhythmia secondary to either digoxin toxicity or
sinoatrial node disease.

16 A. Yes.

17 Q. And then questions sick sinus
18 syndrome.

19 A. Yes.

20 Q. Would you agree with that?

21 A. I think in a broad sense those
22 would be the two leading candidates, or some other
23 rhythm disturbances, be it sick sinus or a similar kind
24 of rhythm conductive abnormality.
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Q. Well, the clinicians --

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A. Recognizing that sinoatrial node disease in the presence of digoxin is much more likely to develop into much more severe arrhythmias at lower concentrations of digoxin than patients without sick sinus syndrome.

Q. Well, trying to narrow down the differential diagnosis, Doctor, if one can. Would you agree with the possibilities that Dr. Costigan has indicated, and I would again indicate to you, Doctor, that the clinicians who have come here and have given evidence have in essence agreed that it was either that or that, one or the other with the question of Dr. Bain and dealing with transient adrenal insufficiency. Forgetting about that for the moment.

A. Well, I don't think that we can completely forget about it in that we still have to cope with some unusual features of both the way this baby handled potassium and his clinical presentation. I agree in the broad sense that the two leading diagnoses, both for which the child would have been admitted to St. Joseph's would have been some sort of rhythm disturbance such as sick sinus syndrome, the second time now that he is going into a pattern that



1
2 resembles what happened at St. Joseph's, one now has
3 to include his original disease process, sick sinus
4 syndrome, or, as you indicated, digoxin toxicity.

5 Q. That's right.

6 A. And we have to be concerned that
7 something else was wrong with the baby which might have
8 explained his potassium and his arrhythmia because
9 even in the face of a normal conducting system,
10 metabolic disturbances, changing movements of ions
11 across membranes can set up the same kind of
12 arrhythmias that quote "sick sinus syndrome can".

13 Q. Well, didn't you give evidence,
14 just dealing with the question of potassium, Doctor,
15 that in children, children get into trouble with
16 digoxin toxicity where there is Lasix or some kind of
17 drug similar to that is given so that there is a
18 withdrawal of potassium from the body because
19 potassium in effect counteracts the effects of
20 digoxin, does it not?

21 A. Except as the potassium begins
22 to go up very high, at which time it enhances the
23 effects of digoxin at the AV node and causes complete
24 block.

25 Q. Well, again, Dr. Costigan has
given evidence that in retrospect he conducted certain



1

2

types of examinations, certain types of treatment to
reduce the potassium level in Kevin's body. There
were three things that he did.

4

5

A. Oh, it doesn't reduce it in the
body, excuse me.

6

7

Q. Well, he reduces it --

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9

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A. What it does is cause a shift
across membrane, and that can be very different
because that shift is also involved at the same site
where digoxin binds.

11

12

Q. Well, an enema would reduce
potassium, would it not?

13

14

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16

A. Kayexolate reduces it very
slowly. The major therapy that he was giving the
child was bicarbonate and dextrose which forces
potassium back across a membrane acutely into cells
and out of serum.

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Q. That is right, but there
was ---

A. The Kayexolate works over a
matter of hours to days. It is much slower than the
effects of crossing back across membranes, and that
is why the acute treatment is given, and the second
treatment to assure continued therapy over time.

Q. But in any event, Dr.
Costigan was concerned after reflection that the
fact that he embarked on this treatment may have
enhanced the effect of the digoxin in his body
because he felt that the potassium may have, in
effect, been combating the toxic effect of the digoxin?

A. It is a very hard balance,
in fact, and there is a great deal of debate in
the literature about what to do. For example, if
you know a patient has an elevated digoxin level,
how to manage his potassium.

The problem again, and I agree
with Dr. Costigan's concerns, I mean, I would be
concerned as a clinician as well that if, for example,
somebody had a very high digoxin level and I caused
him to very rapidly excrete potassium, you know,
multiple diuretics, et cetera, et cetera, I would

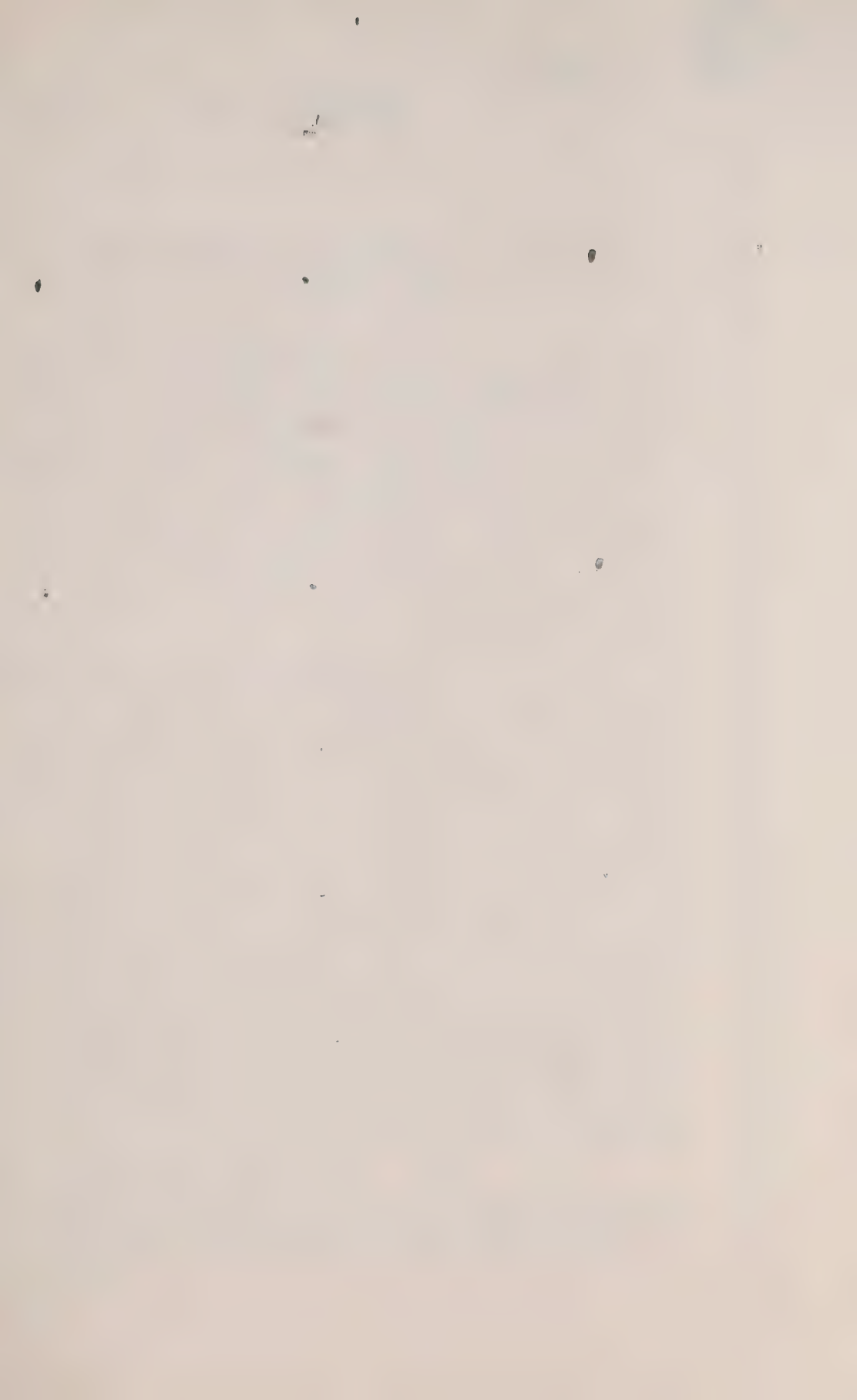


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3 be concerned that hypokalemia or lowering the
4 potassium might enhance toxicity.

5 On the other hand, the reverse
6 also holds and we do not quite understand why that
7 is the case because as the potassium goes up very
8 high, the combination of digoxin and a high potassim
9 can cause complete heart block. So that one is
10 trying to tread a narrow ground of deciding on when
11 to intervene and lower the potassium or to try to
12 raise the potassium.

13 The problem is here, and the reason
14 that I say we are confused to a certain extent, is
15 that we are not quite sure why Kevin's potassium had
16 been a little bit unusual at St. Joseph's and then
17 rose again at the Hospital for Sick Children. We
18 do know that it occurred at both times and that is
19 one of the things that troubles us and why we have
20 to think broadly in terms of other ways that movement
21 of potassium may have been influenced by a disease
22 process or by something else that we do not under-
23 stand or by digoxin toxicity because that has to be
24 considered in the differential diagnosis.

25 Q. Well, that is one of the
things that happens, Doctor, is it not, in the body
where there is an excess of digoxin, that the body





1
2 builds up an excess of potassium to try and fight or
3 combat the effects of ---

3 4 A. No, again, the total
5 potassium in the body is unchanged. What happens is
6 again because digoxin binds to this sodium ATPase
7 sodium potassium ATPase and inhibits it, there is
8 a shift now of sodium for potassium across the
9 membrane with some potassium leaving cell and
10 going into blood, recognizing that when we are
11 talking about potassium we are measuring it not in
12 cells where most of it and most of it is acting, but
13 we are measuring it in blood. So that as you say,
14 if somebody is overdosed with digoxin, accidentally,
15 intentionally, what have you, in a broad sense serum
16 potassium may rise. Serum calcium may also fall
17 as calcium enters a cell, but that is not as reliable
18 a phenomenon in an overall sense.

17 Q. Would it be fair to say,
18 Doctor, that your experience dealing with digoxin
19 and the intoxication of digoxin, as it relates to
20 potassium, that there is more of a situation where
21 there is a lack of potassium as opposed to an over-
22 abundance of potassium?

22 A. In the situations that
23 we are talking about sort of in standard clinical
24
25



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2 use of the patient on chronic diuretics, then in
3 fact, as we indicated, lower levels of digoxin
4 might well be associated with toxicity than in a
5 patient who is not total body potassium depleted.

6 But there we are talking about
7 total body potassium depletion, and here we are
8 talking about what appears to be shifts across
9 membranes because things seem to be going up and
10 down very fast in this baby, and that is a much more
11 confusing circumstance; that is a more confusing
12 circumstance. Again, perhaps the reason that the
13 potassium is high is because of excessive digoxin.

14 On the other hand, the potassium
15 may be high for a totally different reason, perhaps
16 his primary disease which we do not understand, and
17 the digoxin then is, as you will, an innocent by-
18 stander in that pathophysiologic process.

19 That is the problem I have to
20 face when I am dealing with the greater than 10 in
21 this baby in the presence of his survival, then,
22 for two and a half, whatever number of hours and
23 his return into sinus rhythm, because we still have
24 a situation where that kind of level of digoxin,
25 greater than 10, for example, if resulting from
exogenous administration and if at a steady state



1
2 in that the post mortem is consistent with that
3 level, albeit that it may have come down and the
4 postmortem rise may have been more in this baby,
5 I cannot argue against that either because it is a
6 possibility, but given those scenarios, I remain
7 unable to deal happily with that degree of elevation
8 of digoxin and a return to sinus rhythm even in the
fact of the somewhat elevated potassium.

9 Q. Well, let me ask you this,
10 Doctor: in regard to his digoxin levels, you have
11 indicated that there are three possibilities. Number
12 one, that there was an accidental administration;
13 number two, there was an intentional administration;
and number three, there was an abnormal pathophysiology?

14 A. Yes.

15 Q. And would you agree with
16 me on those three?

17 A. Those are the ones that
18 we have discussed, yes.

19 Q. And are there any other
20 possibilities?

21 A. The only other possibility
22 which we always have to consider is artefacts. We
23 have no direct evidence that the samples -- you know,
24 the sample that went to Haematology, we have no
25



1
2 reason to believe that, you know, it was mishandled
3 or anything. We are basically accepting those
4 numbers as such, recognizing that there can always
5 be artefacts, for example, the resuscitation, the
6 pacing wires that were placed, could this elevate
7 the serum digoxin level post mortem? It might, but
8 we have again no evidence directly for that.

9 Q. You are reasonably
10 satisfied on a reasonable scientific certainty that
11 it is one of those three things; is that fair to say?

12 A. Those would be my three
13 leading candidates. I can never be sure beyond my
14 leading candidates. There may indeed be other
15 possibilities which I do not know.

16 Q. Now, I understand as far
17 as this third possibility is concerned that one of
18 the theories, and I believe you expounded that, is
19 that it is a death before death type of thing where
20 part of the body dies and releases
21 digoxin into the blood, and then that causes an
22 elevation of the level in the blood even though no
23 additional digoxin has been given; is that a fair
24 summary of what you said?

25 A. That would be one of a
series of possible mechanisms, others being displacement



1
2 of digoxin by other substances. For example,
3 potassium and digoxin in some circumstances can
4 actually compete for the same binding site, so that
5 if one had some sort of abnormality in handling
6 potassium, conceivably competition between digoxin
7 and potassium could displace digoxin from its binding
8 physiologically without cells dying.

8 Q. Well, you have examined
9 the chart of Kevin Pacsai?

10 A. Yes.

11 Q. Was he administered any
12 of that drug?

13 A. As far as I can see, there
14 was no administration of potassium in the IV or via
15 another mechanism.

16 Q. And there was no incident ---

17 A. But we are talking about
18 endogenous potassium not administered potassium.

19 Q. Well, if I could just ask
20 you about the first possibility, about this death
21 before death, the breakdown of the tissue, I believe
22 you have also given evidence, Doctor, on page 2317
23 at line 8 that you had no hard evidence of the death
24 of any muscle which would cause the release of digoxin?

25 A. Yes, that is true. We do



1
2 not, for example, have an area of an infarct or
3 overt tissue damage in this child.

4 Q. So would that ---

5 A. So that that particular
6 aspect of pathophysiology I would have to say is not
7 high on the list. Then I have to go to a whole
8 series of phenomena related to what regulates the
9 binding of digoxin to its receptor. We put some of
10 those on the board. If I had to guess in the next
11 year, we could fill four blackboards with what
12 regulates ATPase, and both given the problems that
13 the child has with potassium and the problems that
14 the child appears to have with digoxin, I would have
15 to think or invoke a mechanism affecting that
16 particular transport system. What that mechanism
17 is remains speculative, of course.

18 Q. But we know one thing,
19 that there was no death of tissue prior to his death?

20 A. We see no evidence of
21 overt infarcts, that is correct.

22 Q. So that would eliminate
23 one possibility?

24 A. That one of a list of
25 pathophysiologic phenomena, yes.

Q. But you are saying there



1
2 are others on the list that may be applicable in
3 Kevin's situation?

4 A. Yes, as well as many things
5 that we really do not know about. Again, I do not
6 feel I know a great deal about this child. I could
7 speculate as to what could cause his entire syndrome
8 but I do not think that would be helpful.

9 Q. No, we are here hopefully
10 not for complete speculation, although the Commissioner
11 may take that into consideration.

12 Mr. Commissioner, I have several
13 other questions that I intend to ask.

14 THE COMMISSIONER: Yes, you had
15 the good sense not to be here last night so I cannot
16 hold you to any time estimate. However, I am now
17 going to ask you how much longer you will be.

18 MR. SHINEHOFT: I will not be
19 long, Mr. Commissioner. I would hope 10 to 15
20 minutes, and I am prepared to continue if ---

21 THE COMMISSIONER: No, we will
22 break off now and we will come back at 2:30.

23 MS. CRONK: Sir, once again, I
24 have to trouble you with the request that others
25 be asked about time.

THE COMMISSIONER: I think we will



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occupy the afternoon, I would think.

3

MS. CRONK: I agree with you.

4

THE COMMISSIONER: How long do
you expect to be?

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MS. CRONK: I think in culmination
the afternoon will be taken. The only possibility is
that we might finish shortly after the afternoon
break and in those circumstances I do not recommend
commencing the next witness.

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THE COMMISSIONER: Well, believe it
or not I have some compassion.

11

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MS. CRONK: Sir, it was never
in doubt in certain quarters of the room.

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THE COMMISSIONER: All right,
2:30 then.

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---Luncheon adjournment.

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---Upon resuming at 2:30 p.m.

THE COMMISSIONER: Yes, Mr. Shinehoft.

MR. SHINEHOFT: Thank you, Mr.
Commissioner.

Q. Doctor, you indicated in your
evidence, I believe it was yesterday and it is in
Volume 56, Page 2512 - 2513, when you were discussing
the Gary Murphy case; in regard to the question of
pathophysiology, you were asked the question:

"Q. Is Gary Murphy just one exemplifica-
tion of that phenomenon?"

And your answer was:

"A. Yes. There is now published
literature on renal effect and ques-
tions that we have to raise in other
cases we have seen over the last number
of years."

A. Yes.

Q. Do you recall giving that
evidence?

A. Yes, sir.

Q. So is it a fair inference from
your answer that this whole area has been evolving
in the last several years?

A. Really, I suppose within the last



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year or so most of the evidence has come out. There are older published reports which didn't make very much sense until now in light of what we have learned recently.

5

6

For example, some of the defects in renal failure.

7

8

Q. Well, just two questions arising out of that.

9

A. Yes.

10

11

Q. You will agree with me that your answer was that there has been publications in this area over the last several years.

12

13

14

A. Yes. The original reports on renal failure were older, the ones that now begin to give us some kind of idea about mechanism are extremely new.

15

16

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Q. You examined the medical chart of Kevin Pacsai, did you not?

18

A. Yes, I did.

19

20

Q. Did you examine that in regard to the question of renal failure, or lack thereof?

21

22

A. We tried to ascertain if there were any evidence for that. I will have to go back again to the chart in that regard.

23

24

25

Q. Let me say, Doctor, I believe I



1
2 am correctly indicating to you that the BUN readings
3 were normal.

4 A. I believe so, I don't think
5 there was any evidence in this child of abnormal
6 renal function in life.

7 The one thing I should add in that I
8 was not previously aware of because I did not have
9 the microscopic findings of the child's autopsy, I
10 just had the gross pathology findings in my records.
11 I noted in the chart that I have now -- that there was
12 in fact -- when you asked me was there any evidence
13 of any tissue damage at all, yes, in fact there was,
14 there was a cortical infarct in the, in the left
15 kidney, this was thought to be old in that there were
16 areas of fibrosis. There was also some evidence of
17 mild fatty change and hepaticides, again, suggestive
18 of some degree of tissue damage, gave significance
19 to the whole issue. Again, I honestly don't know but
20 I thought we should clarify that point.

21 Q. Okay. Now, you were going to
22 answer me the subsequent question of the renal --
23 you have looked at the coroner's report with regard
24 to this child?

25 A. I had only at that point the
gross, now I have the microscopic as well, yes.



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Q. And the adrenal glands were perfectly normal, in weight and size?

A. I believe the weights were within normal limits, yes, sir.

Q. And there were no abnormalities as far as architecture or size are concerned?

A. There is no mention, sir, wait, I can't find it. Hang on for a second, please. Everything is lumped together as no significant histologic changes. They don't make specific reference to the adrenal as such. They say "other organs including heart, endocrine muscle, diaphragm, intestine, stomach, etc. No significant histologic changes." I assume that includes that as well, I don't know to what extent they were examined.

Q. There has been evidence that there were no abnormalities in the findings.

A. Yes.

Q. You have no reason to disagree with that?

A. No, not at all, I certainly was not present at the autopsy or examined the sections.

Q. Doctor, you have had an opportunity, I believe, to examine the Bain Report, because you in fact wrote part of it, the



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second appendix, is that correct?

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A. The appendix was what I had

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actually put together along with the other people

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in the division, yes.

6

Q. So obviously you read the

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report.

8

A. A long time ago, yes.

9

Q. Did you read the Atlanta

Report?

10

A. Parts of it, yes, the parts

11

that were available.

12

Q. And was there any mention in the

13

Bain Report, or the Atlanta Report of this para-
physiology problem?

14

A. Pathophysiology.

15

Q. Pathophysiology problem as it

16

relates to Pacsai?

17

A. As far as I am aware, no. Most

18

of it, in fact all of it was written before subsequent
literature and papers have arrived.

19

Q. That isn't really true, is it,

20

Doctor. You have just said to us that literature
has been published for a number of years.

21

22

A. There were papers that made, in

23

essence, to us no sense, demonstrating certain

24

25



phenomena which we could not then understand.

The important literature in fact is March 1983 and subsequently, at about the time we then have the opportunity to see the situation with Gary Murphy.

Q. But Doctor, it is fair to say there is absolutely no reference to this in the Bain Report?

A. That is correct.

Q. No reference to this in the Atlanta Report, is that correct?

A. That is correct.

Q. No reference to this by any of the clinicians in their reports?

A. That is correct.

Q. No reference to this by any of the pathologists.

A. That is correct.

Q. No evidence of this by any of the biochemists?

A. That is correct.

Q. And no evidence of this by any of the forensic toxicologists?

A. As far as I know, all that is correct.



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Q. Thank you.

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A. If you are telling me that.

4

I don't know if they read the recent literature.

5

Q. You talked about the question of this necrosis, this dying process of tissue elevating the digoxin level in the body.

6

7

A. As one potential example, yes.

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Q. And the figures, I am interested in the figures that have been demonstrated. I believe you might have an increase of, I think there was one case where it went from 4 to 5.5, is that correct?

10

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A. There was one where we went from a little bit less than 4 to 4.9, to 8, to 12.6.

13

14

Q. Have you ever seen a reading of 72?

15

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A. We have seen levels of 32, which is not very different percentage-wise than 72.

17

18

19

Q. Doctor, please, answer my question. It is a very simple question. Have you ever seen a level of 72?

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A. Since what?

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Q. As a result of this pathophysiology phenomena, an increase from X, unknown, to an increase of Y, which would be 72.

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A. I don't know, in that I am not sure whether some of the high values previously might have been attributed to this phenomenon, I haven't seen any subsequent to the cases that we are discussing today.

Q. I am looking at a subsequent number of 72; have you ever seen that?

A. No.

Q. Have you ever seen a number of 100?

A. No.

Q. Would it be fair to say that the increases are relatively small increases that you have seen?

A. The increases percentage-wise have been rather substantial.

Q. In absolute numbers.

A. In absolute numbers the numbers have been reasonably small, again emphasizing that 32 in terms of the difference in release of digoxin from tissues compared to 72 is probably 2%, 3% or 4%.

Q. Doctor, you have obviously a concern about the whole issue of digoxin, and presumably you discussed this with your colleagues?



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A. That is correct.

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Q. You discussed it with Dr. Rowe?

4

A. Yes.

5

Q. You discussed it with Dr.

Freedom?

6

A. We discussed, Dr. Freedom

7

particularly with respect to the Murphy situation,
yes.

8

9

Q. I am dealing specifically with the
question of pathophysiology.

10

11

A. Yes.

12

Q. Have you discussed that with Dr.

Rowe?

13

A. Yes.

14

Q. Have you discussed it with

15

Dr. Freedom?

16

A. Yes.

17

Q. Have you discussed it with Dr.

18

Fowler?

19

A. No.

20

Q. Now, have you had an opportunity
to read the evidence of Drs. Rowe or Freedom?

21

A. I have not.

22

Q. And do you know if they at any

23

time ever in the evidence that they gave before

24

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this Commission mention this phenomena?

3

A. I believe they deferred to me

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on that subject, at least from discussions with
them.

5

6

Q. Now, Doctor, would it be fair

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to say as a generality, dealing with this whole
area.

8

A. Yes.

9

Q. That firstly, it is a very

10

complicated area of medicine?

11

A. It certainly is.

12

Q. And secondly, as far as Kevin

13

Pacsai is concerned, that he could have died from a
digoxin overdose?

14

A. I have to accept that as a pos-

15

sibility, yes.

16

MR. SHINEHOFF: Thank you, I have no

17

further questions.

18

THE COMMISSIONER: All right, thank you.

19

Now, who is next? Mr. Shanahan?

20

MR. SHANAHAN: I am ready to roll now,

21

sir.

22

THE COMMISSIONER: Yes, all right.

CROSS-EXAMINATION BY MR. SHANAHAN:

23

Q. Sir, my name is Shanahan and

24

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I act for the families of the Dawson and Lombardo
children.

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A. Yes.

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Q. I don't think you specifically
reviewed their charts.

6

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A. No, I have not, sir.

8

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Q. Some of my comments are going to
be general, and I am going to ask you to look at
some of the things that may in fact parallel some of
the other babies.

10

11

First of all, with respect --in
general, I think you spoke with Mr. Hunt about the
theory that Mr. Strathy developed for you, and you
also spoke with Mr. Hunt on the theory of error
occurring in the resuscitation efforts.

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A. Yes.

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Q. But in fairness, sir, my query
to you here, or my quibble with you here, is that as
you look at your discussion of the possibility of
error with respect to these children, would you
agree that other factors apart from sheer numbers
on studies about errors in hospitals, other factors
surely would help you and help other people inclined
to assess whether over this whole time period error
played a large factor?

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A. Yes, indeed.

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Q. Because we have heard evidence, sir, over the months here, about the high rate of deaths; the deaths occurring in a particular locale, that is, on a ward; occurring predominantly at night; the prevalence of certain nursing teams; we have heard them described in many instances as sudden and unexpected, no matter how sick the children were, the particular time of death was sudden and unexpected. You would agree that as the Commission here looks at these deaths that your error theory, or the prevalence of errors has to be modified by this whole set of circumstances and the whole context of these errors and how they keep repeating themselves.

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A. I think the situation that we both face, all of us face, is that in fact we are dealing with what appears to be -- and again, I can't speak to the epidemiology, but what at least appears to be a changing pattern in deaths on the ward. The problem is how we relate those deaths to the digoxin data which we have.

22

23

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Q. Exactly.

A. And then can we in any way make the extrapolation that the digoxin data we have



1
2 are vital to the pattern of deaths, an epiphenomenon
3 by which I mean something that happened at the same
4 time as the deaths, but not directly causally
5 related, or simply something that we presently don't
6 understand.

7 The issue being that for each of the
8 individual children, unless we are sure how each of
9 them got the digoxin, and how each of them ended up
10 with the numbers that they got to, we cannot be
11 sure that in fact the digoxin data represents a
12 pattern similar to the pattern of the deaths on the
13 ward.

14 In other words, if one or two children
15 have reasonable biologic explanations for the digoxin
16 levels that they had, what then does that do to one's
17 epidemiology. If one child, for example, is an
18 artefact, shall we say, the struggle then that all
19 of us face is what does that do to our interpreta-
20 tion of the relationship between the levels and the
21 overall pattern of mortality.

22 Q. Quite apart from that, what I
23 am saying to you is, whereas at one time there
24 may be an error in dose, and another time a drug
25 may be substituted and digoxin instead of
some other drug.



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A. Yes.

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Q. Whereas another time the

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wrong baby may get it; that at the same time as

5

we have an overview that perhaps you as one witness,

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with respect, don't have, you will agree as I recite

7

some of the other factors which seem to keep cropping

8

up; the similarity of team; time of death; place

9

of death and what have you, that surely your numbers

10

when placed against that backdrop of this commonality

11

of factors you would have to agree that your error

12

theory, if you like, has to be weighed against these

13

other factors that we have seen.

14

A. I think we have to be terribly

worried about the epidemiology, of course.

15

Q. Another thing, too, sir, it

16

would strike me error, by definition, would be random

17

in terms of place, and time and personnel and drugs,

18

that error would happen from the top to the bottom of

19

the hospital with many drugs, some toxic and some

20

non-toxic, with nurses, with doctors, error would

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not necessarily, I would have thought by definition,

22

start to localize itself on a ward at a time with

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a certain personnel, with a certain drug.

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A. Errors in fact do cluster that way.

Q. I appreciate you have given some very good examples.

A. The racemic epinephrine, for example, and, again, the types of errors and the drugs involved are going to be very dependent on the types of patients on the ward, the number of drugs being administered, the frequency of that drug being administered throughout the ward. For example, if a drug is given to a very percent of patients, the chance of a patient perhaps not on the drug receiving that is greater than if the drug is used, say, in one out 50 patients.

So the epidemiology, if you will, and I am not an epidemiologist, perhaps I shouldn't use the term, but the error rate with the specific compound is going to be very much dependent on the clinical nature of the ward, the drugs used, the numbers of patients, the busyness on the ward, how well the drugs are stored on the ward and, thus, one expects significant differences in both the numbers and the quality and the specific types of errors that you would see on different wards. For example, on the adult wards you would never see a mistake between



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vitamin E and racemic epinephrine, neither one would
3 be used.

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Q. All right. Not to follow that

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too far, sir, but in terms of - we have heard when

6

Dr. Costigan searched the hospital that apart from

7

certain areas where it wouldn't surprise us if it

8

wasn't present, we will say a cancer ward, that there

8

was digoxin in many diverse areas of the hospital?

9

A. Yes.

10

Q. That adults and infants at

11

various times received it?

12

A. Yes.

13

Q. In terms of timing, we have

14

seen graphs and studies, sir, that have come up to

15

our particular Commission period and we have seen

16

studies from after our Commission period and then we

17

have seen what happened when digoxin was locked up

and when a certain nursing team was disbanded.

18

Now, you would agree that when you tie

19

those factors into your error theory that your error

20

theory, if you like, has to be weighed against these

other factors that we have seen?

21

A. In the deliberations of the

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Commission you are going to have to consider everything.

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Q. All right.

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A. Pharmacologic, whether the pharmacology indeed demonstrates uniformity or not and whether the pharmacology has a relationship between everything else. That I certainly can't differentiate.

Q. All right, sir. Now, finally, sir, in terms of a person, be it a nurse or a doctor committing an error, and I am certainly not saying you are an apologist here for the hospital, but as I look at it again, sir, your error theory could really well nigh explain anything. It first of all can explain too high a dose getting into a child?

A. Yes.

Q. It can explain a child in a neighbouring bed getting a dose?

A. Yes.

Q. I would have thought, as I looked at one of my children, Lombardo here, that it couldn't explain the Lombardo child never having supposed to have been on digoxin getting it, but then again, the more I thought about it if the error was large enough that too could be explained?

A. I am not quite familiar with the data on this infant, so I can't comment on the amount, sir.



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Q. Well, right. But that could happen by a child in a neighbouring bed or room on digoxin, Lombardo being given that dose?

A. Yes.

Q. And if you were open minded enough or liberal minded enough for it, to coin a word, if you were naive enough, if you even came upon somebody administering digoxin to a child that wasn't supposed to have it, you really could, if caught in the act, you could really accept an explanation that indeed, whoops, it was an error?

A. I think that would probably be the first explanation that one would come to, yes.

Q. All right. So, really, by that theory, sir, you would have to have a child on that ward who was perfectly normal anatomically, who wasn't prescribed digoxin at all and who you would have to have someone caught in the act of giving an overdose of they were getting a therapeutic dose after all, it could be someone else's?

A. Yes.

Q. But getting an overdose?

A. Yes.

Q. And, so, that error theory would only break down when we would have that situation



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where you couldn't accept an explanation from a person
that in fact they were getting, say, Baby Jones - is
that right, you nodded yes?

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A. I am not quite sure I understand
the question, but if I understand it that the only way
that one can come to a very high assumption of
intentional administration would be to indeed witness
somebody giving an unacceptably high dose, so much so
that it would be impossible to accept error.

10

Q. Error, that's right.

11

A. Yes.

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Q. All right. Sir, if you would
just look at some of the chemical things that you high-
lighted about Baby Pacsai. As I reviewed Lombardo's
chart, some of them came up and if you could have
given to you Exhibit 78 which is Baby Lombardo's
chart. I will only be a moment sir, I just want to
look at some of this and get your reaction to it.

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We were told, sir, by Dr. Rowe that
Baby Lombardo had come in there on the first day of
birth and had had an operation to put a shunt in its
heart. It stayed in the ICU, it came down to the
ward, was on the ward one day and died on the ward.

22

A. Yes.

23

Q. The operation was successful,

24

25



1
2 was not on digoxin. I think Dr. Vera Rose indicated
3 that digoxin might even be contra-indicated in this
4 child. It was being infused with heparin through
5 an IV.

6 A. Yes.

7 Q. Now, on page 102 of the charts
8 that you have we have the last clinical chemistry
9 report. Have you got that page, Doctor?

10 A. 102, yes, sir.

11 Q. 102. Now, the first column is
12 December 22nd, 1980 and the timing of that, or the
13 hour of collection appears to be 10:20.

14 Now, we know, sir, that from other parts
15 in here that on December 22nd, that would be that day,
16 at about an hour later, 11:15 the child was taken out
17 of ICU and back into the ward. So, these would be
18 the last samples, as I interpret this, taken when the
19 child was in the ICU. Now, there are not too many
20 results there, but one is potassium at 4.8.

21 A. Yes.

22 Q. All right. Now, at 11:15 on
23 December 22nd the child comes back onto the ward and
24 then passed the midnight hour. It is really not on
25 the ward a full day, if you know what I mean by a
26 24 hour day, the 22nd from around noon onwards it's



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on and then at 3:30 in the morning of the 23rd it goes into arrest and dies.

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A. Yes.

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Q. Now, the 23rd of December, and there is no time indicated.

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A. Yes.

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Q. So, I don't know in terms of at the top there, hour of collection, I don't know how accurate these are, if this would be done around midnight or some time between midnight and the hour of arrest at 3:30. But in any event, it appears that there are tests on December 23rd and it is those results, sir, that I wanted to look at with you and get your reaction to.

14

15

Now, Dr. Costigan was struck by the rise in Pacsai's potassium level.

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A. Yes.

Q. Somewhere in the 4's up to, I think Pacsai went to 7.7.

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A. Yes.

Q. And that caused him concern and it led him to make the common query how the potassium got that high when it wasn't prescribed or given to the child.

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A. Yes.



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Q. And then he was concerned about the high dig. or the high potassium linking up in some way with the high dig.

A. That is correct.

Q. Now, if Pacsai goes to 7.7 so quickly, it seems to me that in less than 24 hours, and maybe less than 12 hours, depending upon when the second sample is taken, that young Lombardo has gone from 4.8 to 7.4?

A. That is correct, the potassium increases from 4.8 to 7.4.

Q. All right. And as I gathered here, over the 7 you are high, it is very high?

A. Yes, this is a high potassium.

Q. All right. I notice here, do you see anything, sir, in the 7.16 pH. It strikes me that that was very acidic?

A. Yes. Now, you have to realize I haven't gone through this chart.

Q. No, I do appreciate that.

A. So, I am working at big clinical deficit here.

Q. All right.

A. The pCO₂ was 68, the baby was not breathing. I believe with that kind of pCO₂ the



1
2 baby is in bad straits. In other words, he is
3 beginning to retain carbon dioxide, his pH is
4 extremely low at that time. When, again, we are
5 dealing with such large changes in pH it is not
6 inconceivable, but again, we are dealing with exchange
7 across a membrane for potassium. If in fact this is
8 an intra-arrest sample, which again I don't know.

9 Q. I am going to let you complete
10 here.

11 A. Sure.

12 Q. You said that to Mr. Shinehoft
13 about Pacsai because you said to Mr. Shinehoft that
14 Pacsai's was peaking and going into a valley.

15 A. Yes.

16 Q. And therefore the potassium
17 may be just across the cell exchange.

18 A. Yes.

19 Q. But before you go on on that
20 and I forget and don't follow up on it, as I looked at
21 previous potassium readings in the previous week here
22 they are all pretty steady, 4.5, 4.2, 5.6, 3.8 and
23 4.8.

24 A. Yes.

25 Q. There has been, you will agree,
no peak and valley that we have seen in Pacsai.



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A. Now, you know, again, I don't

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know this infant.

4

Q. I appreciate that, but just on

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pure numbers there.

6

A. Yes.

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Q. The potassium seems to be

8

regular.

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A. It appears that there seems to

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be no problem here.

11

Q. All right. I interrupted you

sir, so, go on.

12

A. Yes. The two issues, and again

13

I don't know when the sample was drawn, if I had to

14

make a judgment about when such a sample would have
been drawn, I would say that, and again I don't even

15

know what the baby's downhill course was like or

16

subsequent course.

17

Q. Yes.

18

A. But either this would be intra-

19

arrest or at a time when the baby was already in,

20

shall we say, extremist in that the pH is low, the

21

pH02 is very high and if the baby is already in the

22

process of quote "dying", I can't interpret the

23

potassium because the potassium is going to be coming

24

out of cells all over the body.

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Q. Yes.

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A. In addition to which the very

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low pH by itself may acutely elevate the potassium.

5

Without knowing the exact details and without knowing

6

when the sample is drawn relative to the baby's course,

7

it becomes very very difficult. The clue to something

8

very very very bad going on in the baby at this point

9

is that the pCO₂ has gone extremely high and the pH

10

has gone very low; both of which then become

consistent with an elevated potassium.

11

Q. pH has gone very low. I thought

12

you said very acidic, 7.16?

13

A. It has decreased. Normal blood

pH is 7.40. 7.16 is acidotic. In other words --

14

Q. There is no calcium information

15

on this, as I see it?

16

A. There is no calcium information.

17

Q. And that BUN reading of less

18

than 5?

19

A. That's normal assuming normal

muscle mass and protein intake, yes.

20

Q. All right. So, would you share

21

what Dr. Costigan felt about Pacsai, at least on first

22

blush that on a child who has been fairly constant the

23

previous week with respect to his potassium, that

24

25



1
2 within a very short time it's gone to a very high
3 level.

4 THE COMMISSIONER: I am sorry, did you
5 mean Pacsai?

6 MR. SHANAHAN: Yes. Pacsai,
7 Dr. Costigan said clearly about the sudden rise in
8 potassium and I am saying to you that on just that one
9 isolated issue, chemically, does not Lombardo here
10 seem to have gone overnight to an extremely high
11 potassium?

12 THE WITNESS: They are very different
13 and the reason I think that Dr. Costigan raised the
14 question in terms of potassium was that at the time
15 that potassium was taken that baby was not in the
16 extreme state that this baby appears to be from the
17 remainder of the blood gases. The baby did not have
18 a pCO₂ of 68, did not have a pH of 7.16 at that
19 moment.

20 MR. SHANAHAN: Q. I see.

21 A. When that was taken. And, as
22 such, again, because if you look at potassium as an
23 issue there is a tremendous amount intra-cellularly
24 and a tiny fraction extra-cellularly and in the
25 extreme clinical situation which this blood gas
suggests that this baby was in, i.e., in an extremely



1
2 bad clinical state, perhaps even intra- or post-arrest,
3 under those circumstances, yes, indeed, you can get
4 dramatic changes in potassium in very short periods
5 of time.

6 So, it is a different clinical setting.
7 Beyond that, again, to be fair, not having gone through
8 the chart in detail and not knowing when this blood
9 level was drawn I don't think we can say much more
except that it is a very different setting.

10 Q. All right.

11 A. At least according to the
12 chemistry.

13 Q. Pacsai has got a high
14 potassium reading when ostensibly the child is not as
15 sick as you think Lombardo is?

16 A. Yes.

17 Q. Lombardo was an extremist, it
18 would be sick and everything would be out of whack?

19 A. Yes.

20 Q. And the potassium being out of
21 whack here you don't think really --

22 A. Would not be unusual. For
23 example, a potassium drawn most times intra-arrest or
24 during resuscitation processes, we tend to ignore it
25 again because the baby is an extremist, the chest may



1
2 be pumped manually to get the heart going. This again
3 raises potassium artificially. So that we can't
4 really say much about it further than that, sir.

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Q. Finally, then, to deal with this potassium bugaboo, if you like, we have heard that there seems to be kind of certain unique features, but it seems to be one of them that you mentioned here today again was that you have seen -- there seems to be the phenomenon that high potassium seems to be seen at times when you do have dig. toxicity?

A. That certainly can occur.

Q. And that the effect of the two is that it quite often leads to heart block?

A. Well, let us again try to clarify that issue. First we have to deal with the concept of total body potassium and where that potassium is, inside cells or outside cells.

In a situation of dig. toxicity, digoxin toxicity, there will be a tendency for the serum potassium to rise because of inhibition of this enzyme that we have been talking about all along, the sodium potassium ATPase, so that certainly an elevated potassium is one potential sign of digoxin toxicity.

Now, in that setting, if one then administered additional potassium and forced the potassium perhaps even higher, there is the



2 1
2 risk that in fact the two combined together will
3 lead to heart block. This is this delicate balance
4 issue we are talking about where a low potassium,
5 particularly low total body potassium after a patient
6 has used diuretics for a long period of time, will enhance
7 digoxin arrhythmias and at the same time what seems
8 to be paradoxical if you force the potassium up too
9 high by administering potassium which normally would
10 be thought of as protecting the heart, if you force
11 it up too high you end up with heart block. So we
12 are talking about an intermediate ground where it
13 is going to be dependent both on the body stores of
14 potassium and what potassium is actually being
15 administered to the patient, and how much is going
16 out in the urine. So it is a balance issue.

15 Q. If I can just tell you
16 that Lombardo has no potassium given to her, she is
17 not on diuretics; as I said, the only drug she is
18 on is heparin, you have seen the charts for the
19 previous week's reading, they are in the normal
20 range, and you have seen that within 24 hours she
21 has high potassium, and you have said she may well
22 have been an extremist, we do not know?

22 A. Yes, and in fact under
23 those circumstances the potassium can rise in a
24
25



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2 matter of minutes.

3 Q. But you have also said
4 that we have seen the phenomenon of high digoxin
5 accompanying high potassium?

6 A. Certainly.

7 Q. Finally, another thing
8 you said with respect, I think it was one of the
9 five that you did study, was you said that the
10 very effect of dig. on the heart, that is making
11 it contract slower and stronger if you like, it in
12 itself can sometimes lead, the mechanics of digoxin
13 working on the heart, can sometimes lead to a high
14 potassium reading. Did you make that comment or did
15 I get you wrong?

16 A. I think you must have
17 misinterpreted me. If I did, it was in error.

18 Q. All right. I find
19 an error on my part.

20 In this situation finally
21 here, sir, about the confusion of drugs, do you know
22 anything about heparin, what it looks like or how
23 it is stored?

24 A. Yes, in fact we had a
25 little bottle of hepalean which we provided to the
Commissioner.



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Q. All right, I could have missed it, I am sorry.

A. I am not sure again, the bottles of hepalean and digoxin in there are little green labels on them. They look almost identical. In fact, that was the one I had difficulty reading yesterday because the vial was turned around.

Q. Sorry if I am wasting Commission time. Could you just point them out to me and that will end this line of questioning for me.

A. Okay. This one ml green vial, I am going to have to look again, is digoxin. This little green vial is heparin. Now, that does not apply there.

Now, the one thing I have to add into that is that I am not exactly sure of the colouring as of March 1981 because some things do get changed in vial colours, and I know that digoxin was that colour. I am not sure about hepalean and whether that may have changed, but at least the current preparations are identical sized vials with identical colour lettering.

Q. All right. I will take it upon myself to check that one out.



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Finally, sir, with respect to Lombardo, we have only exhumed tissue readings, and I think somebody pointed out to you yesterday, Mr. Strathy pointed out to you that as an appendix to the Bain Report there was a comment with respect to substance X coming up and the possibility of the presence of substance X not only in blood during lifetime but perhaps also in tissue, exhumed tissue?

A. Yes.

Q. I just wanted to speak to you about that. First of all, I think you have agreed that if we have the technique of mass spectrometry as we now know it, you seem to be reasonably certain that if we identified digoxin as real digoxin you accepted that it was real digoxin?

A. Yes, again with the caveat if the substance ended up having a similar mass spectrum we are going to have to change our minds.

Q. Another factor is, sir, as I recollect it -- other counsel may correct me -- that this Dr. Seccombe, the most that he ever found in terms of his reading I thought my recollection was 4.7 nanograms, was the highest reading of this substance X that he ever found?

A. I do not believe we have tissue levels, at least my understanding of his



1
2 publication was only serum levels so that we do
3 not know anything about tissue.

4 Q. He did not have any in
5 tissue. Then are you aware, and you probably are,
6 that on Mr. Cimbura's limited testing and when he
7 used the purification and the extraction techniques that
8 he had, that in fact he never came across this
substance X, he never found ---

9 A. That I do not know. If
10 other people do, in fact technology may be different,
11 patients may be different, et cetera.

12 Q. And then finally, a
13 position to put to you, sir, here is that other than
14 this substance X, if it does exist and if it is not
15 simply a difference in technique, in purification
16 techniques, that if in fact it exists, chemically
17 it may well be coming off the assay in a confusing
18 manner such that it resembles digoxin, but I think
19 you have agreed that you do not know whether it
20 shares with digoxin all the other properties, and
specifically, that multiplier effect in tissue; you
just do not know?

21 A. At this stage we have no
22 specific data with respect to that.

23 Q. Finally, the last child
24
25



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2 is Dawson. Amber Dawson was a child that was 11
3 months old. I think she is one of the eldest, but
4 not the eldest of the children we are studying.

5 She died in July of 1980. I
6 think she is the very first child whose death was
7 so sudden and unexpected that the coroner is actually
8 called in and the autopsy finds no anatomical cause
9 of death.

10 These are facts I give to you,
11 if you can accept them here for the sake of argument.
12 The child came into the Hospital because of failure
13 to thrive and after five days in the Hospital on the
14 ward and before any surgery was undertaken, the child
15 died suddenly.

16 Now, in terms of errors, sir, I
17 have it that the mother of this child administered digoxin
18 to this child practically its whole life, and surely,
19 then, the proper dose, the proper digitizing dose
20 and the proper maintenance dose would have been
21 assessed, the mother would have given it without
22 error and she being an untrained, unmedical person.
23 What does that do to your theory about the errors
24 that can come about administration?

25 A. Hospitals are different
than homes and one's children are different than the



1
2 children one takes care of in hospital. The settings,
3 in fact, are grossly different.

4 We try very hard to educate
5 parents of chronically ill children how to care for
6 their children at home and how to carefully measure
7 up digoxin, for example, or another drug. What we
8 usually do, for example, is provide them with
9 syringes that have a specific line on them, usually
10 a heavy, thick black line, instructing the families,
11 usually the nurses do this as well as the physicians,
12 instructing the mother how to draw up the specific
13 medicine, she goes to the drug store, it is dispensed
14 by the pharmacist, how to draw that medicine up to
15 the line and how to assure that she delivers it
16 satisfactorily to her child.

17 She is administering one drug
18 to one child. She does not have 30 syringes sitting
19 around. She does not have hundreds of medicines
20 sitting around. She does not have to open vials
21 of medicine. She does not have to dilute medicines.
22 She does not have other responsibilities on the ward
23 to other children. It is a very, very different
24 setting.

25 MR. SHANAHAN: I see. I have no
further questions, thank you.



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THE COMMISSIONER: Thank you.

Mr. Tobias?

CROSS-EXAMINATION BY MR. TOBIAS:

Q. Doctor, my name is Warren Tobias and I act for the family of Jordan Hines.

I believe before lunch in cross-examination by my friend Mr. Labow, you indicated that with respect to the drug digoxin its toxic effects were more likely to take place where there was an increased risk of them taking place if an appropriate dose were given in a child with a damaged heart?

A. Yes.

Q. Is the opposite of that correct that a child with an anatomically normal heart or a perfectly normal child who perhaps might not even be in a clinical setting would be expected to have perhaps a better tolerance to the drug?

A. Yes, that is generally stated in the literature. We have had experiences where, for example, a two year old child ingested his grandmother's digoxin pills, arrived in hospital with a blood level of 14 nanograms per ml which would, from most people's point of view, be considered an exceedingly high level, with only minor symptoms,



10 1
2 some degree of heart slowing, and in fact by the
3 time his blood level was down to about 7 nanograms
4 per ml he was entirely well.

5 Q. So that it is possible
6 with respect to a normal child that if one were to
7 give a child in that condition a normal maintenance
8 dose of digoxin, it might not show any effects at
all?

9 A. Yes. In fact, if you
10 took a reasonable number of children and administered
11 a therapeutic dose of digoxin, for example, in error
12 or what have you, one would expect to see reasonably
13 little. Similarly, even in a child, for example,
14 with heart disease, if he was not particularly ill
15 at the moment, again you might well expect a small
16 dose not to have any therapeutic consequences at
17 that time. In fact, you might miss the fact that
it had happened.

18 Q. I believe you also gave
19 evidence to Mr. Roland yesterday that there were
20 recorded instances in the literature, or I should
21 not say recorded instances in the literature, there
22 were instances where perhaps drug errors were not
23 reported simply because they were not serious drug
errors and had no effect?

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A. Yes.

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Q. And that could certainly

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happen with digoxin, could it not?

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A. Yes, and in fact it

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happened at least in one instance on 7F during the
racemic epinephrine episode.

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Q. In the ordinary case, and

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I realize that that itself is a rather vague term

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because every case has its own particular unique

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characteristics, but as a general rule, a child on

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digoxin therapy, and we are talking now about a

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neonate, under one month old, how many doses a day

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of digoxin would that child reach once he was on
the maintenance level?

14

A. The standard approach now

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is usually dividing the daily doses into two separate

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doses. Some people give it once a day. I believe

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that most of the dosing done on the patients during

18

the time in question and still at the moment would

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be dividing the dose into every 12 hours or twice
a day basically.

20

Q. Right, and what would the

21

general accepted dosage be?

22

A. Very, very broad dose

23

range. Many children will be in the range, say, from

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12 2 5 to 10 micrograms per kilogram per day divided into
3 two doses. So that an average dose might be, say,
4 5 micrograms per kilogram per dose maintenance.
5 That would be a rough starting point.

6 Q. Now, just so that I under-
7 stand this, assume that we have a 4 kilogram child,
8 you are saying the standard dose, then, would be
9 20 micrograms?

10 A. 20 micrograms per dose,
11 yes, or 40 micrograms total per day.

12 Q. Exactly, administered 12
13 hours apart, perhaps?

14 A. Exactly, yes.

15 Q. Now again, with respect
16 to our healthy child who perhaps is not even in
17 a hospital setting, I take it that if one were to
18 administer two times a day a therapeutic dose to
19 that child, that child might be expected to go on
20 for several days before he showed any signs of
21 reaction to the drug at all; is that correct?

22 A. I think it is certainly
23 possible, yes.

24 Q. Okay, fine. With respect
25 to the situation where toxicity does begin to show,
what would you expect would be the range of



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concentration that you would have to give in order to get toxicity in a normal child? In other words, let us say I doubled the dosage and gave it four times a day, would you then expect perhaps to see some adverse effects setting in fairly quickly?

A. I think it is very, very hard to predict.

Q. Would it depend on the individual child, Doctor?

A. It would depend strongly -- I mean, on average it is said in the literature that hearts in the paediatric age group, if we can use that expression, tend to be reasonably more resistant than, say, older hearts in general, but the range of variability is going to be vast.

Q. All right, let me ask you this question, then. If we had a child with an anatomically normal heart and that child were on a regular therapeutic dose, even at the high range, the high end of the range as to what would be therapeutic, and if it were administered twice a day, one certainly would not expect one or two or even three or four doses over a 24 to 48 hour period to be fatal, would one?

A. All else being equal and



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assuming the child is indeed healthy and is simply
put on a maintenance dose of digoxin, probably not.

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Q. Now, in the ordinary case where one has a child with heart disease and one wants to reach a maintenance level on digoxin, I understand that the first process you go through is where the child is digitalized; is that correct?

A. Yes.

Q. Now, I don't have too much understanding of that term, doctor, and perhaps you can help me.

In order to digitalize a child, what exactly takes place? Are they given more frequent injections or higher amounts? Exactly how does one digitalize in trying to build to a maintenance dose?

A. The issue again is one of trying to fill the total body stores, as we have explained, so that, at a volume of distribution of, say, 15 litres per kilogram, we will end up with a therapeutic type concentration. What one does then is back calculating, based on that approximate volume of distribution, how much you would like to give. It will vary with age.

I can give you one possible scenario which would be somewhere in the neighbourhood of 40 micrograms per kilogram. Now, that will be a



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total digitalizing dose, for example, in a specific child. The range is broad. Sometimes in smaller children, particularly premature infants, one will want to go much more gradually; in other situations one might want to go a little bit higher. Let us use 40 micrograms per kilogram --

Q. All right.

A. -- as the first daily dose.

One usually does not give that as a single dose, again because of concerns about giving too rapidly a dose and such and wanting to assure oneself that the child isn't going to get into trouble with the dose.

The standard practice is dividing the dose in half, giving half a dose as a starting dose. Then, over the next 24-hour period giving two-quarters of the remaining dose. So that you will give, for example, 20 micrograms per kilogram; twelve hours later, 10 microgram per kilogram; twelve hours later -- 20, 10 and, then, 24 hours after the first dose, 10 more. So, you will have 20 micrograms per kilogram; twelve hours later, 10 micrograms per kilogram; twelve hours later, 10 micrograms per kilogram.

Q. So, in other words, in your scenario, you would have three injections given over



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the period of 24 hours; in total, 40 micrograms per kilogram?

A. Yes. This would be for a standard patient.

Q. Is it fairly rare that they will digitalize the child with one dose?

A. I think it is probably very rare. The situations where one might push a little bit more rapidly might be a situation with cardiac arrhythmia, dysrhythmia, where sometimes such disturbances in rhythm, in order to be broken, shall we say, or converted back into a regular rhythm, require somewhat higher levels of digoxin than one would use in a failing heart. So sometimes, one would proceed more rapidly in that type of patient.

Q. Now we have talked about the term "steady state".

A. Yes.

Q. And as I understand that term the way you have explained it to us, steady state is that state that you reach when the particular dose of digoxin is fully distributed and, at that point, about 99.5 per cent of the total volume of digoxin that was administered is then in the tissue?

A. Yes.



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Q. It is fair to say, however,
that from the period of the acute phase, of the alpha
phase, all right, what you have in seconds to minutes
when the concentration starts to drop off --

A. Yes.

Q. -- from that point until
you reach the beta phase there is an ongoing distribu-
tion process taking place?

A. Yes, with clinical effects
as well.

Q. Fine. So, you would expect,
let us say in the middle of that phase, or one-third
into that phase, or a quarter into that phase, you
would expect to find some level of digoxin having
already been delivered to, or distributed to, the
tissues?

A. That is correct.

Q. And obviously the other
side of the coin is whatever had not been distributed
would still be in the serum?

A. Or in what we call the
central compartment.

Q. Or in the central compartment.

A. Yes. Part of which is serum.

Q. And you would be able to



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measure that?

A. Yes.

Q. Through immunoassay?

A. Yes, through measuring the serum concentration.

Q. Now, if we had a child who was healthy, with an anatomically normal heart, who had not been given a digitalizing dose at all but who was given a therapeutic dose, would you expect that it might take quite some time before you would see blood concentrations or, rather, concentrations in the serum that would be measurable by RIA?

A. From an initial therapeutic dose --

Q. Exactly, assuming no other administration at any other time.

A. That is the correct dose for that particular child?

Q. Correct.

A. Again, we would have to know the specific level of sensitivity of that assay --

Q. Right.

A. -- and how low you can indeed go. It might be detectable but you would expect it to be, as I say, quite low.



1
DD6 2 Q. You would expect it to be
3 quite low?
4 A. Yes.
5 Q. It is theoretically possible,
6 is it not, depending on the sensitivity of the assay,
7 that you might have the less than .2?
8 A. I think it is conceivable
9 we could back calculate, but it is conceivable.
10 Q. Now, with respect to your
11 particular theory that you posited here on drug
12 error, as I understand it, what we have got is the
13 following: We have a situation where drug error,
14 in your view, certainly is not unlikely to happen
15 during resuscitation efforts. That is one possible
16 scenario?
17 A. That is one possible time,
18 yes.
19 Q. You also indicate that it is
20 not that uncommon for the wrong drug to be given to
21 the wrong child. Example in point, a dose of digoxin
22 is intended for child A; there is a mixup and that
23 is given to child B.
24 A. Yes.
25 Q. As I understood it, the
third scenario that you posited basically for drug



DD7

error is where there is simply a drug mixup. One intends to give, let us say penicillin and instead digoxin is given.

A. Yes.

Q. If we can, just for a moment turn to specifics.

I wonder, Mr. Registrar, if you could put before the witness Exhibit 103, which is the medical record of Jordan Hines.

I understand you probably have not had a chance to review that medical record.

A. No. Again I have not been able to, in detail.

Q. I won't ask you very many detailed questions on it.

Doctor, let me assist you by giving you some facts which I would just ask you for a moment to accept.

A. All right.

Q. The first fact is that this particular child, Jordan Hines, first arrested at about 4:10 a.m. on March 9, 1981. I believe that the resuscitation efforts with respect to this child - we have the pat evidence put before us that those resuscitation efforts went on somewhere between two



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and two and a half hours,so that the child was pronounced dead shortly after 6:00 a.m.

A. Yes.

Q. I would ask you to turn with me to page 83 of the medical report of Jordan Hines. It would appear from that page, doctor, that there was only one administration of drugs on March 8, 1981 and, on March 9, 1981, there was no administration of drugs to that child.

The question I would like to ask you is this: Assuming that an error happened on March 7th, at which time there were certain administrations of drugs given, I believe in total some six or seven administrations, in fact.

A. Yes.

Q. Assuming that an error had been made back on March 7th --

A. Yes.

Q. -- and assuming it was just a one-time error, all right, that the child received a normal therapeutic dose of digoxin rather than the prescribed drug of gentamicin or ampicillin --

A. Yes.

Q. And again assuming that this child had a structurally normal heart - and



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evidence has been put before the Commission that was the case - you certainly would not assume from that one administration in error for there to be either a toxic or a fatal effect which would show up sometime on March 9th, would you?

A. That is presupposing that somebody calculated a correct maintenance dose of digoxin for the child?

Q. Yes.

A. It is something of an unlikely error. It would mean that they would have had to misread the order and calculated something that was not on the ordersheet and then administer it.

So, that is a bit of an unlikely scenario, I believe.

Now, the question is whether the volumes of either gentamicin or ampicillin, if one for example had confused them --

Q. Yes.

A. -- or, for example, confused babies - one getting ampicillin and one getting digoxin; put the digoxin in one and ampicillin in the other - that scenario becomes very difficult to deal with in that we would not know what kind of doses we were talking about. They could have been



Spielberg
cr.ex. (Tobias)

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very large relative to the babies' size, or very small; we really would not know.

Q. Perhaps if you turn with me to page 76 of the medical record.

A. Yes.

Q. You may get some assistance. There appears to be an ordersheet on that page, the second one down - unfortunately it is undated - whereby ampicillin -- is that 200 micrograms?

A. Milligrams.

Q. Milligrams?

A. Yes.

Q. -- gentamicin, 10 milligrams

A. Yes.

Q. -- by IV --

A. Yes.

Q. -- were, presumably, the prescribed volumes of those two drugs.

A. The prescribed number of milligrams.

Q. I'm sorry, correct.

A. Yes.

Q. Now, let us assume that the way the error happened - just for the sake of argument for a moment - is that digoxin was mistaken



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DD112 for ampicillin. I would take it that basically
3 what would be administered in that particular situa-
4 tion would be 200 milligrams of digoxin.

5 A. No.

6 Q. All right. Explain to me
7 what the more likely scenario would be, if that error
8 were made.

9 A. Okay. And again we are
10 really totally hypothesizing here.

11 Q. Okay.

12 A. 200 milligrams of
13 digoxin, of course would be somewhere in the neighbour-
14 hood of 400 vials of adult digoxin, and I doubt if
15 that could ever be quickly obtained.

16 Q. Right.

17 A. Now, the more standard
18 error would be, if we are talking about this kind
19 of error - and again ampicillin doesn't come in a
20 vial like digoxin; so, we are dealing with a very
21 different scenario. The more typical error would be
22 making a mistake and confusing the volume of one
23 drug for the volume of another drug. So for
24 example, one would draw what one thought might be
25 ampicillin and in fact it was digoxin; so you
would end up with a volume of digoxin equivalent to



DD12

1
2 the amount of ampicillin you wanted to give originally.

3 Q. Yes.

4 A. Now, I am sorry, I don't
5 have information with me about concentrations of
6 ampicillin and volumes and such; so I can't really
7 comment on that.

8 Q. Perhaps I have misunder-
9 stood, doctor.

10 A. Yes.

11 Q. Perhaps you can help me.
12 In administration of a drug like
13 ampicillin, I take it that it is not diluted when it
14 is drawn?

15 A. No. Most of the ampicillin
16 comes in a powdered form --

17 Q. All right.

18 A. -- in a multi-dose vial,
19 and what you have to do again, is draw up whatever
20 solution you are going to solubilize it in.

21 Q. Yes.

22 A. Then add that and mix well
23 and then draw up your ampicillin.

24 Q. And I take it it is unlikely
25 that would be done in the patient's room? That
would be prepared back where they keep the medications?



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DD13 2 A. It would be usual to prepare
3 in the medication room. And again I am not sure
4 about the layout on the floor at that time. There
5 are some situations where vials of medications will
6 be kept in a room so that the nurse would not then
7 have to leave the room. I think, realistically,
8 although it certainly could happen - and we have
9 seen more bizarre things happen, in fact - confusion
10 with the multi-dose vial of ampicillin with an
11 ampoule of digoxin. I think would be a bit unlikely -
still possible but --

12 Q. You agree it is possible
13 but unlikely to happen?

14 A. Yes. Yes, I think so.

15 Q. You also I believe, have
16 said that one of the reasons, I believe, for that
17 conclusion is that digoxin and ampicillin come in
entirely different kinds of vials?

18 A. Yes.

19 Q. How about gentamicin?
20 Would it be easier or less easy or would it be the
21 same scenario; that it would be highly unlikely to
confuse gentamicin for digoxin?

22 A. I don't remember how
23 gentamicin is dispensed. I would have to check a
24 CPS to see that.
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Q. Is it -- again my same question would be, with respect to gentamicin, is it a powder?

A. Again, I'm not sure if that comes already soluble. I'm sorry. We would have to look that up.

Q. All right. Perhaps you could and you could advise Mr. Roland, who will then pass that information on to me.

A. Certainly. I will be happy to.

Q. All right. Fine.

THE COMMISSIONER: Would this be a good time?

MR. TOBIAS: I'm sorry?

THE COMMISSIONER: Would this be a good time?

MR. TOBIAS: Yes. I was about to move on to another area.

THE COMMISSIONER: Yes. All right. We will take fifteen minutes.

MR. TOBIAS: Thank you.

--- recess.



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---Upon resuming after the recess.

THE COMMISSIONER: Yes, Mr. Tobias.

MR. TOBIAS: Q. Yes, Doctor, just before the break I was about to move on. If I could go back for a very quick moment just to clear up one particular area in which I am confused. You have indicated to me that with respect to ampicillin, to the drug ampicillin, the reason why it is highly unlikely to mistake that for digoxin is due to the physical makeup of the drug itself, that it is powdered and it has to be mixed in solution.

A. Yes, certainly to mix up the vials is unlikely.

Q. Is unlikely, okay. Now, with respect to the drug gentamicin, you told me that you really don't know what kind of a vial it comes in or form.

A. No.

Q. So, you really can't comment on how likely it is to mistake that drug for digoxin. But if we can just talk for a moment about the volumes.

A. Yes.

Q. I would take it that the drug, gentamicin, which I understand to be a very commonly



prescribed drug.

A. Yes.

Q. Is not very highly diluted;
in other words, its concentrations in whatever container
that is in would be fairly high.

A. Again, I really don't remember the
concentrations per ml. in the vial.

Q. But would it be higher in con-
centrations than in a drug like digoxin which is used
in very, very small amounts?

A. No. It certainly would be
higher than the concentration of digoxin, I would
guess.

Q. Okay.

A. Again, in that we are dispensing
digoxin in micrograms and a drug like gentamicin
in milligrams.

Q. All right. Now, assuming for
the moment and, you know, when you tell Mr. Roland
and he passes the information on to me we will find
out whether this assumption was a fair one or not,
but just for the moment let us assume that gentamicin
comes in a vial that is similar to digoxin.

A. Yes.

Q. And they are both in soluble



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form.

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A. Yes.

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Q. Is it very likely that one can

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mistake the digoxin for gentamicin and draw up a

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quantity of 10 milligrams; in other words, how

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much dig. would you have to draw up?

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A. Well, you could not draw 10

milligrams out of a digoxin vial.

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Q. Okay. And that is because the

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concentration is so low, correct?

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A. Yes.

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Q. All right. How many ampules

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would you basically have to go to to draw up 10

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milligrams of digoxin?

A. 20 ampules of adult digoxin.

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Q. So, on that basis, that kind of

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error, I take it, would be highly unlikely.

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A. No. Again, the issue is not

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milligrams, okay. For instance, let's say that this

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amount of gentamicin, and again I don't know,

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represents a half cc.

Q. Yes.

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A. Then if you drew up a half

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cc. of digoxin you would end up with 250 micrograms.

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Q. All right. I see your point.

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A. So, if you had two identical

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vials, okay, you believed one of them to be digoxin,

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you would draw up the volume that you expected to be

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correct for the gentamicin, you would end up with

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whatever amount of digoxin was present in whatever

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volume that was.

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Q. I see. So that in other words

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what you are saying is that you would have to know

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how many cc's 10 milligrams of gentamicin is.

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A. Yes.

12

Q. All right. Knowing that, then,

one could tell how likely the mistake might be.

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A. Within limits.

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Q. All right. If it is, for

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example, 10 ml., which I don't think it is, but if

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it were 10 ml. and the vial of digoxin is only

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2 ml., obviously you can't do it. If it is 2 ml. or

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less there could indeed be the possibility of such
an error.

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Q. All right.

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A. But I think it is better to get

the hard information before we speculate on it.

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Q. I understand. Now, going back

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to what we were talking about before, which was

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the various possibilities or scenarios for an error

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in administering the medication.

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A. Yes.

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Q. We have talked about the possibility of drawing up the wrong drug, mistaking one drug for the other.

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A. Yes.

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Q. Let's talk for the moment about the possibility where dig. intended for another child is given inadvertently.

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A. Yes.

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Q. All right. Now, we know by looking at the medical record of Jordan Hines, Page 83, that it is unlikely that a mistake of that sort could have happened on March 9th because there is no indication on the medication and treatment record of any prescribed drug being given to Hines on the 9th. Do you agree?

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A. In terms of confusion of one medication for another, no. In terms of potentially receiving somebody else's medication because of patient misidentification, sure, possible.

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Q. All right. So, what you are saying is it is certainly possible that he could have been given digoxin meant for someone else and they could have signed in that other patient's



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record?

A. Exactly.

Q. All right. Now, another possibility, of course, is that on the 8th we see that there was an administration of drug to Hines.

A. Yes..

Q. Possibly a mistake could have occurred then in that the dig. intended for someone else was given to Hines.

A. Yes.

Q. All right.

MR. ROLAND: Mr. Commissioner, I may be missing something, but as I understand it Jordan Hines died on the 8th, so, of course, he wouldn't be given anything on the 9th. The record is that Jordan Hines died on the 8th.

THE COMMISSIONER: Yes, he did, he died at 6 a.m. on the 8th.

MR. ROLAND: So, I don't know what my friend is talking about.

MR. TOBIAS: You are quite right, Mr. Roland. You are quite correct.

Q. There was one administration only on the 8th of drugs for Jordan Hines.

A. Yes.



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Q. It is possible that some mix up

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could have occurred on the 7th, I take it.

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A. Certainly.

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Q. Now, with respect to the kind

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of error that we have been talking about, I am

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asking you now to draw upon your own experience.

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The most likely scenario for that kind of error, I

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take it, would be where a drug is given to a child, the

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drug being intended for someone in another bed in

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the same room.

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A. Possibly, that would be one

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potential scenario, sure.

14

Q. Now, do you agree with me that

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if a child were in isolation in a room by itself the

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margin for that kind of error goes down.

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A. In a general sense if a child

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is in a room by himself there is obviously much

19

less chance of his receiving his roommate's drug,

20

sure.

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Q. All right. Obviously, it

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still could happen.

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A. Sure.

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Q. Becuase in fact he might re-

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ceive a drug intended for the child in the next room



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but it is unlikely to happen.

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A. Again, it would depend very

much on the nature of the way in which the drug is
travelled around the ward, the administration trays,
how the syringes and such were grouped together.

Q. All right, fine. Now, with
respect to another question asked you this morning
by Mr. Labow, and that was if the impairment of the
circulatory system would tend to lengthen the alpha
phase, in other words, slow down the half-life of
the drug. Now, you indicated that you really don't
have any good information on that.

A. No, we don't have any hard
data, I'm sorry.

Q. Okay. Now, I take it, however,
that basically the job of the circulatory system,
to use Mr. Lamek's analogy, is that of a transport
system.

A. Yes.

Q. It is the blood flowing through
the system which delivers the particular drug to the
various tissues.

A. Yes.

Q. All right, to the extent, for
instance, that we have cardiac arrest where there is



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a complete stopping of the pumping of the heart and a complete halting of the transport system, we would not expect, I take it, in that situation to still have ongoing distribution of the drug after that point because the very system that carries it has stopped moving.

A. Assuming complete cessation of circulation, yes.

Q. All right. Now, I know that you say that you don't have any hard scientific evidence on the point, but is it a fair assumption that if you had a markedly impaired circulatory system in that the blood moving through the system had been slowed down considerably, that you would get less effect of distribution to the tissues?

Is that a fair assumption?

A. It isn't yet. The problem being that we don't know the avidity of the receptor for withdrawing digoxin from serum. The scenario or the difficulty comes in, for example, with certain types of drugs and how well the liver can remove those drugs from circulation. There are some drugs that are very quickly removed by the liver actively and those drugs tend to be rather independent of blood flow. There are other drugs which enter the



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2 liver passively and those drugs are very much
3 dependent on liver blood flow.

4 Now, that has been well demonstrated
5 for the liver for a variety of different drugs. What
6 we really don't know, and the reason that I have to
7 say I don't know what effect changes in circulating
8 status would really have with respect to distribution
9 is we don't know the relative extraction capacity of
10 tissues for a drug from blood obviously, in the
11 extreme situation, as you suggest, no circulation,
12 no further distribution, tremendously impaired
13 circulation. It is not unreasonable to think that
14 distribution is going to go down but to what extent
15 there are probably so many variables that we couldn't
16 predict with any degree of accuracy.

15 Q. Would it vary from organ to
16 organ?

17 A . It might well because, again,
18 during certain aspects of either cardiac failure
19 or under circumstances where circulation is impaired,
20 otherwise blood flow may be preferentially distributed
21 to some organs and less so to others. So, again,
22 our predictability falls further.

22 Q. All right. Now, with respect
23 to a situation where you have no recordable blood
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pressure at all. Do I take that to mean that in effect the circulatory system is stopped entirely or could we still have circulation even in a situation where we could not record blood pressure?

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A. I can't really give you good physiologic figures. I mean, again, that is a bit beyond my realm in terms of what goes on in the process, for example, where an individual's circulation has stopped, one is providing external cardiac massage, some blood is flowing but blood pressure is exceedingly low.

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So, under those circumstances, there may be some degree of circulation with rather minimal blood pressure. The extent of that and how effective that would be, say, at delivering drug I think is so hypothetical that we really can't say.

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Q. All right, fair enough. Now, with respect to the fact that blood pressure has dropped to a level at which we cannot record it, and taken into account the factors that you just elucidated, is it fair to assume that what we do have is markedly impaired circulation?

A. Yes.

Q. All right. I would take it of



12 1 a fairly significant degree?

2 A. That would be the general assump-
3 tion, yes, sir.
4

5 Q. Again, I ask the same question.
6 Would it be a fair assumption that that markedly
7 impaired flow somehow impairs the ability of the
8 system to deliver the drug to tissues such as
9 heart tissue in particular?

10 A. Again, I think we lack information
11 to the extent that I can't really answer directly.
12 It would obviously to the heart be dependent on
13 coronary blood flow which might be rather different
14 than systemic blood flow and, again, we have to deal
15 with the relative capacity of tissue to extract drug,
16 even under circumstances of reasonably poor flow.
17 In other words, if ultimately the question comes down
18 to what kinds of tissue levels does one expect under
19 different scenarios of administration with respect
20 to changes in circulation, the bottom line is, I
21 don't think we have the data in any way to answer
22 that and, if we did, my guess is that there would be
23 so much variability that we would be talking about
24 mean or median situations with such a range on each
25 side that in honesty I wouldn't know how to interpret
it.



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Q. All right. Now, I believe as well before the lunch break Mr. Labow asked you regarding the ongoing distribution process during the alpha stage.

A. Yes.

Q. And I think the exact example that he used was that given the fact that there are five half-lives in that stage of distribution, if basically in each half-life it was 20% of the total volume of digoxin that was being delivered.

THE COMMISSIONER: No, no, we have had that out several times.

MR. TOBIAS: All right.

THE COMMISSIONER: First half-life is 50%.

MR. TOBIAS: Yes.

THE COMMISSIONER: Second half-life is 50% of what remains.

MR. TOBIAS: Yes.

THE COMMISSIONER: Third half-life is 50% of what remains and, strangely enough, somehow or other they get the whole, but I don't think that is correct. I haven't figured that one out either yet.

MR. TOBIAS: That is precisely what I was having trouble understanding.

THE COMMISSIONER: It is like the frog that



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jumps half way across the pond and he keeps on doing it and the small child is then supposed to figure out when he gets to the other side.

MR. TOBIAS: Q. Is it a fair assumption on that basis that after the first half-life, which I think would take about a half an hour.

A. Broad range, yes.

Q. Could we say with any certainty that 50% of the total load had been delivered, or might be less than that?

A. Again, we don't have hard numbers to say, yes, 50% of the drug is now bound and 50% of the drug is still in the central compartment because we still don't understand what the essential compartment is physiologically. Some of the essential compartment may be accounted for by binding, some of the essential compartment is accounted for by body water, some of it by serum, some of it by erythrocytes, red cells, excuse me, and the issue is not knowing that we are dealing with pharmacologic constructs, not anatomical regions. What we do know that it is, that after one half-life the serum level has now come down to one-half and the major issue responsible is distribution of that drug into a variety of different tissues.

Q. All right. Is it fair to say,



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then, that it would be quite difficult to make any sort of projection or calculation of precisely how much quantity of digoxin one would find in tissue, even if we knew the specific kind of tissue we were looking for, like heart tissue, only from being told the length of time after administration?

A. Yes. We have already said it is steady state, there is at least -- and this is steady state -- there is at least ten-fold variation between serum concentration and tissue concentration; at least ten-fold variability. That, not taking into account all the other variables which we have been discussing now in terms of time.

Q. All right. Taking all of those other variables into account, it would be a pretty dicey proposition, would it not, to try and estimate on any different phase of the beta phase exactly how much concentration of the drug had reached heart tissue.

A. At any phase in general we have a major problem interpreting those numbers.

Q. All right.

A. It may be very rapid in one patient, it may be very slow in another patient, depending on whether it saturates enough at all,



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it might be highly variable in terms of the final
number you end up with.

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The point we have been trying to make
all along is because of that variability that's
the quandry we are in.

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Q. All right. Now, specifically
with reference to a question asked you the other
day by Mr. Lamek I believe the evidence is that with
respect to Baby Justin Cook, from the time of the first
intercardiac injection to death was about 24 minues.

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A. Yes.



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Q. Now, that obviously is only a portion of the alpha phase, in fact it is about one half life.

Can you, with any reasonable degree of certainty, really predict what kind of tissue concentration of digoxin you would have after 24 minutes?

A. Again, that is our quandary. We cannot say whether 1100 is well within that range or outside that range. The problem again being that in any calculations in that infant we are still dealing with a massive quantity of digoxin on a microgram per kilogram basis, far more than one would give as a loading dose which we said would be a total of 40 micrograms, given his 20, 10 and 10. In this situation we are dealing with a scenario where we are talking perhaps 50 micrograms, perhaps 100 micrograms per kilogram as a whole adult vial, and it is not unreasonable to imagine a scenario with that amount of drug where you could achieve 1100.

I do not know to what extent that might happen, and that is why we have to say we cannot tell whether that drug was given at moment X, at the time of arrest, infra-arrest or at some point before arrest.

Q. Now, I believe in answering



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Mr. Lamek's question what you said is that it is pharmacologically possible, or I think your own words were pharmacologically reasonable that you might get tissue concentration of that sort within 24 minutes. The only point that I make is in light of your last couple of answers, obviously, all you can do is postulate. You really cannot give an answer to that question with any degree of certainty?

A. With a total amount of drug which might have been given up to certain limits, it is not an unreasonable number to have reached in the least. Whether that was in fact what happened, one cannot say because in fact in all of these calculations, and just to emphasize it again, pharmacokinetics can take us only so far in this argument. This is everybody's frustration. If it could take us further, we would obviously perhaps not all be here now.

Q. Now, you have given evidence before this Commission about the strives made scientifically in learning more about digoxin, both in the detection of digoxin, testing for it, the way it reacts in the body.

I understand that between March of 1981 and today it has become routine practice in the hospital on deaths to assay for digoxin; is that



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correct?

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A. I believe so, yes.

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Q. Now, given the improved

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technology, if you like, if I can use that word, I

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would take it that most of these tests, in any event,

7

are done under what you would today consider optimal
conditions?

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A. They are done under clinical

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circumstances where things have been -- an attempt has

10

been made to as much as possible control variables,

11

recognizing again that this is not like doing an

12

experiment in a laboratory.

13

Q. Now, between March 1981 and

14

today, do you know if there have been any deaths at

15

the Hospital for Sick Children which were attributed
to digoxin toxicity?

16

A. Which were attributed to

17

digoxin toxicity?

18

Q. Yes.

19

A. I really cannot answer that

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directly.

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Q. Is that because you have no

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knowledge of it?

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A. I have no knowledge. You would

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have to ask the cardiologists with respect to that.

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Q. All right. You certainly have not heard that any deaths have been attributed to digoxin toxicity, however?

A. But that would not mean much.

Q. No, that does not mean that none have been. I am just saying you have no information for us?

A. No, I cannot provide you that information.

Q. Now, with respect to the child Jordan Hines himself, I think your evidence has been fair. You have indicated to us that you would have to accept as of today that if digoxin was found on the assays, it was probably administered during life, subject to the caveat about substance X, and you indicated to Mr. Lamek that you still might change your mind.

Is it fair to say, though, that because we do not have a serum level on Jordan Hines we cannot really say anything with any degree of accuracy at this point about the amount of dig. which might have been administered during life?

A. Yes, we can say nothing with respect to amount or route: oral, IV, what have you.

Q. And for all of those reasons,



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we really cannot say much regarding the time that it might have been administered?

A. We can say nothing with respect to time.

Q. Nor can we say whether the amount administered would have been toxic?

A. No, we cannot.

Q. Or if it caused or contributed to the death?

A. No, we cannot.

Q. We really cannot answer any of those questions with any degree of scientific exactitude; is that correct?

A. That is correct.

MR. TOBIAS: Those are all the questions I have for this witness, Mr. Commissioner.

If I may be so bold, I believe, sir, that I was this time only 29 minutes.

THE COMMISSIONER: Well now, with that noble example, Mr. Roland?

MR. ROLAND: I will follow it up with no questions.

THE COMMISSIONER: Now Miss Cronk?

MS. CRONK: Thank you.

THE COMMISSIONER: I think I have one



1
2 question for you. You mentioned that in the steady
3 state there are ten times as much digoxin in the tissues
4 as in the blood?

5 THE WITNESS: No, what I meant by that,
6 sir, is that the studies that -- you have several of
7 the manuscripts, and that little chart that I prepared,
8 in fact there may be even three-hundredfold or more
9 greater in tissue, but the variability from one
10 patient to another, if you had a serum level and a
11 tissue level that is tenfold, for example, you can have
12 a blood level of 1 and have a tissue level of 100 or
13 1,000, so that the predictability, even assuming steady
14 state, and we do not have to take into account all the
15 time variables, is tremendous.

16 THE COMMISSIONER: What I am really
17 getting at, though, is whether it is almost invariably
18 at steady state, though; in order to be steady it has
19 to be greater obviously in the tissues?

20 THE WITNESS: Yes.

21 THE COMMISSIONER: And you are talking
22 about all of the tissues, are you not? You are talking
23 about all of the tissues at this point?

24 THE WITNESS: Most of the variability
25 studies have been done in heart. I would expect the
exact same thing in the other tissues to a more or



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less extent in all of them.

THE COMMISSIONER: Just taking an example, for instance, you have a level of 1 in the serum in steady state.

THE WITNESS: Yes.

THE COMMISSIONER: You have a level of 10 or perhaps 100 in the heart.

THE WITNESS: Yes.

THE COMMISSIONER: You could have a level of 10 or perhaps 100 in the brain, in the liver, in any place else?

THE WITNESS: No, the amounts are quantitatively set on a nanogram per gram basis and vary tremendously from tissue to tissue and even vary from different parts of the heart.

THE COMMISSIONER: I understand that. It is not going to be the same?

THE WITNESS: Yes, but you would expect ranges, yes indeed.

Those studies have not been done, but based on everything that we know about the nature of the binding sites, similar kinds of compounds and the nature of biologic variability in general, one would expect to see a substantial amount of variation again for reasons we do not completely understand either.



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2 THE COMMISSIONER: All right. Yes,
3 Miss Cronk.

4 RE-DIRECT EXAMINATION BY MS. CRONK:

5 Q. Dr. Spielberg, you have told us
6 in the last several days about a number of instances
7 at elevated digoxin readings that have been recorded
8 at the hospital since the events of March 1981.

9 A. Yes.

10 Q. And I would like to address your
11 mind to those and mine for a few moments.

12 You have told us about a child that has
13 been described here as Child A, and that child or
14 patient was again discussed this morning, and you have
15 told us that that child had antemortem digoxin readings
16 of 4.9, 5.6 on the immediately next day and then 8,
17 as I understand it, two days after that; do I have
18 that correctly?

19 A. No, not exactly, and again, we
20 have a nanogram/nanomole situation that we have to
21 deal with. The initial level was in the range, and
22 again I did not bring those data with me today, was
23 in the range of slightly less than 4 nanograms per ml;
24 then without any digoxin administration went up to
25 4.9 nanograms per ml; then subsequently that day after
initially rising in the morning, the level went up



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2 further just at the time of the child's arrest to
3 about 8 nanograms per ml and postmortem to 12.6, I
4 believe it was, or 12.5.

5 Actually, Dr. Phillips has all of the
6 data on those children on the computer output that he
7 provided you, except for the previous level, the lower
8 level from which the digoxin level increased the next
9 day and then increased at the time of the child's
arrest.

10 Q. Doctor, thank you, that is very
11 helpful. I would simply like to be clear about the
12 information that is currently available to you on that
13 child. Dr. Phillips will be here next week and will
14 be testifying, and we can enquire of him further.

15 Do I understand what you have just said,
16 then, in reciting all of those levels that those levels
were all measured in nanograms per millilitre?

17 A. Yes. The problem is they were
18 originally reported in nanomoles and we have been
19 trying to convert them back for you.

20 Q. And what was then the 5.9 level
21 that you had indicated earlier this week?

22 A. Again, we are going to have to
23 go back. Can I see if we can find the actual data
24 within here? That might be helpful so that we can get
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exact numbers.

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Q. All right, perhaps we will move on and we will deal with the second child, and if you do have the information available to you, then perhaps you can provide it to me. I am interested, as well, in obtaining the autopsy number in that child.

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A. Yes.

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Q. Doctor, then, with respect to this child, are you in a position to help us as to whether or not the child exhibited any symptoms of digoxin intoxication prior to death?

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A. As far as we were aware, the child was in the intensive care unit on a monitor. We did not see any evidence of digoxin toxicity in the child at the time.

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Q. And Doctor, you have told us that in respect to both the liver and the kidney in that child, there were what I believe you described as severe toxic indicators in both of those organs?

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A. This is correct.

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Q. In your own mind when you became aware of the elevated digoxin levels that had been recorded on the child, were those levels explicable by the kidney and the liver failure that was evidently being experienced by the child?



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2 A. The first thing we obviously
3 were looking for was administration, since the level
4 had gone up in the absence of administration.

5 Finding no evidence of that and finding
6 evidence in that child of one, hypoxia as a result of a
7 pertussis infection in his lung, and two, the
8 fact that several different organs were exhibiting a
9 lot of damage as we could assess by blood chemistries,
10 liver and kidney, our best assessment at that time was
11 indeed that the digoxin appeared to be derived probably
12 from those forces and indeed continued to rise over
that period of time.

13 Q. All right, Doctor, I appreciate
14 that when confronted with levels of that kind one would
15 naturally at the hospital attempt to explain them by
16 examining every reasonable scientific possibility, and
17 my question to you was is it your opinion, having
18 regard to the levels that were in fact recorded, that they
19 are explicable, given the state of the kidney and the
20 liver in that child and the circumstances concerning
his or her excretion ability at the time of death?

21 A. Not excretion here, again,
22 because there was no continued administration. The
23 level was going up despite no administration.

24 Q. I am talking about the ability
25



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2 of the kidney and the liver to function, Doctor. Was
3 there a problem with either of those organs sufficient
4 to account for elevated levels in your mind?

5 A. Function, no.

6 THE COMMISSIONER: Which child is this?
7 Is this child --

8 MS. CRONK: Child A, Mr. Commissioner.

9 THE COMMISSIONER: Child A, yes.

10 THE WITNESS: The difficulty, again,
11 being that we are dealing with a situation where even
12 if you totally shut off liver and renal function, okay,
13 and there is no further administration, then the amount
14 of digoxin in the body is going to remain more or less
15 constant within some degree. There may be other
16 routes for excretion, and with the total amount in
17 the body remaining the same, then one cannot talk
18 about excretion; one has to talk about some
19 phenomenon related to either redistribution, which
20 seemed to us to be the most reasonable explanation
21 under those circumstances, or another pathophysiological
22 phenomena which we cannot yet define.

23 Q. Doctor, I am concerned, as well,
24 about the possibility that when a child who has
25 received digoxin and digoxin is then stopped but the
child is experiencing kidney shutdown or renal



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2 misfunction whether or not the digoxin can effectively
3 accumulate in the child's body such that when the first
4 level is taken, as in this case, the level might be
5 4.9, but when a subsequent level was taken the digoxin
6 has continued to accumulate because the body has been
7 unable to permit excretion of the digoxin
8 concentrations and the level is higher; is that
9 possible in your view?

10 A. Accumulation is dependent on
11 continued administration. If you have, let us say,
12 for example, a patient who has been given digoxin
13 chronically and let us just say, for example, on day
14 15 his level is 2, we then decide to stop the digoxin;
15 now, we could calculate from a level of 2 what his
16 total body store of digoxin would be. He cannot get
17 any more digoxin to accumulate. There is no source
18 for the digoxin to accumulate. He has got what he has
19 got in his body, in essence.

20 Then the issue is what happens over the
21 next period of time.

22 THE COMMISSIONER: It will not go out
23 via the blood is what you mean?

24 THE WITNESS: There is no way it can
25 get out now, assuming -- and there is no way that
further digoxin can come in and accumulate. and there



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2 is no way we are going to create digoxin.

3 MS. CRONK: Q. Doctor, I think I
4 understand your point. So that in the circumstance then
5 of this child, the fact that the levels did in fact
6 elevate on three separate testings suggests to you
7 in those circumstances that the elevation and the
8 continued concentration of digoxin cannot be explained
9 based on the kidney and renal state of the child,
10 that there is some other explanation?

11 THE COMMISSIONER: There has to be.

12 MS. CRONK: Q. Have I not put that
13 fairly, Doctor?

14 A. No, we have to talk about two
15 separate phenomena when I am talking about kidney and
16 liver in this child.

17 Q. Let me see if I can put it more
18 fairly, Doctor, and if I have not, please feel free to
19 give the explanation.

20 We have heard in evidence from other
21 witnesses, and perhaps you will agree with this and
22 perhaps you will not, but we have heard that one
23 possible explanation for elevated digoxin levels is
24 kidney shutdown or renal failure?

25 A. Precisely.

Q. And that, I take it, is not a



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relatively new scientific discovery. That has been
commonly accepted for some time?

A. This is a well known phenomenon.

THE COMMISSIONER: That is dependent
on administration, continued administration?

THE WITNESS: Yes, dependent on
continued administration.

MS. CRONK: Q. I understand the
Doctor's point. The purpose of my enquiring further
with respect to this child, Doctor, is that I would
have thought that hypothetically, at least, it was
possible that, because we have heard errors can be
made in terms of the time of sampling, that sample 1
could be taken prematurely with the result that there
is an aberrant level recorded?

A. In which case it would have
been higher.

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Q. Yes. In which case,
presumably, it is higher.

A. And now it goes higher
still two days later.

Q. And then it is higher
still. In those circumstances, given that no further
digoxin was administered to this child, that explana-
tion, at least the possibility that that was an
explanation, kidney shutdown or renal failure
doesn't seem to explain this case. That is really
my only point.

Okay. Let us look at two different
things --

THE COMMISSIONER: I think you
could just agree with that, couldn't you?

THE WITNESS: Well, no.

THE COMMISSIONER: She has now
come around to your point of view and I think you
would like to agree with that.

THE WITNESS: I would like to agree
that it is not excretion, but what I was speaking
with respect to in terms of kidney and liver damage
was death of cells releasing digoxin as a mechanism
for providing digoxin now to increased serum con-
centrations. I wasn't, here, talking about the role



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of the kidney and the liver for excretion of digoxin from the body.

MS. CRONK: Q. I see, doctor.
Then I did misunderstand you.

A. Okay, but from tissue damage.

Q. In respect then of child A, I take it then that in a clinical sense, there was no indication of a malfunction of the kidney or liver in terms of their excretion duties in the body?

A. That was also occurring.

Q. Perhaps we have taken that one as far as we can, doctor.

May we turn - and I think I am trying to be fair; I do understand your position now. There are two interrelated things that were occurring in that child.

A. Okay. If I can try to simplify it in two sentences.

If excretion of the drug is impaired and continued administration occurs, the level of the drug will go up - okay.

Q. Yes.

A. If administration does not continue in the face of either damage to tissues



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as well as simple release of digoxin from those tissues, as well as by the fact now they can't be excreted, so we have got now a situation where we have the same amount of drug in the body but organ damage, we get redistribution and rising levels despite the fact that no digoxin has been administered.

Q. I understand, doctor.

May we turn, then, to child B.

A. Yes.

Q. Child B that you have discussed.

THE COMMISSIONER: The two minutes was not too long.

MR. ROLAND: Long sentences.

MS. CRONK: Doctor, I am not going to look at the clock for ten minutes but I promise you I will then.

Q. Dealing with child B, a again you have explained to us with respect to that child that he or she was also in the ICU.

A. Yes.

Q. And that he or she had severe congenital heart disease.

A. Yes.

Q. As I understand it.



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A. Yes.

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Q. And again digoxin was

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stopped.

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A. Yes.

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Q. And, again you have a

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situation where the levels appear to elevate over a
period of two days.

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A. It was approximately two

9

days, yes.

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Q. Now, in that situation

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doctor, I believe you told us that the patient was
going into renal failure.

12

A. That is correct.

13

Q. I take it, in that context,

14

you were referring to excretion ability?

15

A. Yes.

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Q. In that context, doctor,

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let me deal first with the levels. You have told

18

us that the day before digoxin was stopped, the
level was 6.

19

A. The day after digoxin was

20

stopped the level was 6.

21

Q. All right. The day after

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digoxin was stopped it was 6.

23

A. Yes.

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Q. And two days after that

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it was 11.

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A. Yes.

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Q. Were those measurements

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in nanograms or nanomoles?

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A. I believe nanograms. I
would have to check to be one hundred per cent sure
on that because there has been a lot of confusion
in the reporting systems.

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Q. Perhaps you could check

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and let us know.

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A. We will have those charts

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available for you.

14

Q. And, doctor, in terms of
the clinical position of that child, can you help us
again. Was there -- I'm sorry, were there any
symptoms exhibited during life of digoxin toxicity
of that child before he died?

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A. As far as I am aware, with

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the discussion with the Intensive Care Unit people,
the child did not exhibit standard symptoms of
digoxin toxicity. He had cardiac problems and

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severe heart disease. I don't remember, in that
specific episode, what the terminal type of arrest
pattern was in the child.

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GG6 2 Q. But it is not your impres-
3 sion that it was considered that the patient was
4 exhibiting what would traditionally be regarded as
5 symptoms of digoxin intoxication at the time of
6 death?

7 A. He was exhibiting what the
8 staff in the ICU felt was attributable to his
9 heart disease. Again, with the caveat that one
10 cannot be one hundred per cent sure, given the over-
laps, but they did not attribute it to digoxin.

11 Q. Doctor, once again having
12 regard to the fact that this child was going into
13 renal failure, was there, in your view -- did the
14 state of the child's renal function and the state of
15 the organs involved account for elevated digoxin
levels in this child?

16 A. Again, on a simple excretory
17 basis, not so terribly easily because again we
18 don't have evidence of ongoing continued administra-
19 tion, which would have led to arrival at a new higher
20 level.

21 There are data in the Annals of
22 Internal Medicine, which, I believe, the article has
23 been submitted already. In renal failure, not only
24 can excretions stop but again whatever phenomena -
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redistribution or other pathophysiological phenomena appear to occur again with rising digoxin levels. Again we don't fully understand why that is. It appears to be now a phenomenon that has been reported from multiple centres, certainly not only our own experience - talking to other centres, and the published literature, people are beginning to recognize this more.

Q. Well doctor, with respect to this child --

A. Yes.

Q. -- you have told me with respect to child A there were two problems.

A. Yes.

Q. There was difficulty in terms of cellular death in the kidney and the liver and there was a difficulty with the excretion capacity --

A. Yes.

Q. -- to function.

A. That's right.

Q. In the second case, in child B, we know he was going to renal failure.

A. Yes.

Q. There was a problem with the



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ability of the system of the body to excrete.

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A. Yes.

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Q. Was there as well an

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issue in your mind of tissue death with respect to

6

either the kidney or the liver?

7

A. Unfortunately, in this

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child, we did not have an autopsy, so we don't know

9

what extent of tissue injury contributed to the

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elevation. We only have the renal failure, which

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we felt, again, not on the basis of now not being

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able to excrete the drug necessarily, but by changing

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its distribution primarily we had the rise because,

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again, only affecting excretion in the absence of

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continued persistent administration. Here, we have

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no persistent continued administration. Excretion

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then traps the same amount of drug in the body,

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again within limits, and now we have a rise in

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Q. Are you saying that renal

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failure, because of whatever happens to the kidneys,

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may actually increase the digoxin level?

22

A. Yes.

23

THE COMMISSIONER: It may?

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THE WITNESS: Yes.

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GG9

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2 THE COMMISSIONER: I can't see how,
3 but it could?

4 THE WITNESS: The article in
5 Annals of Internal Medicine again speculates - and
6 this was an important article because it came out at
7 about the time of Murphy - that either substances
8 accumulating from renal failure displace digoxin
9 from binding sites or, in some manner which again
10 we don't really understand, changes the apparent
11 volume of distribution, which means that, when we
12 measure it now, the volume in which the drug would
13 have to be dissolved has shrunk, the interpretation
14 generally being a redistribution of digoxin, perhaps
15 somewhat akin to what happens post mortem with
16 redistribution but again we don't understand all
17 the variables at all.

18 MS. CRONK: Q . Doctor, we may
19 be closer together than I originally thought.

20 In that situation then that you
21 have just described --

22 A. Yes.

23 Q. -- you had a case, a concrete
24 example of a child in the Hospital whose digoxin
25 levels were elevated notwithstanding the cessation of
digoxin therapy --



Spielberg
re.dr. (Cronk)

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GG10 2 A. Yes.
3 Q. -- and there was evidence
4 of renal failure within your mind, for whichever
5 reason you happened to prefer as being most likely,
6 which appears to have accounted for the elevation
7 in the levels?
8 A. Yes.
9 Q. Doctor, then may we refer
10 to child C, and you recall this perhaps better than I.
11 A. Yes.
12 Q. This is a child who
13 unfortunately suffered a severe form of skin disease.
14 A. Correct.
15 Q. Once again you told us
16 that there was a level after digoxin had been stopped
17 of 4.4.
18 A. Yes.
19 Q. And five days later it
20 was still 4.4.
21 A. Yes. It had gone from 3.7
22 to 4.4.
23 Q. And then remained constant
24 five days later.
25 A. Yes.
Q. Again in that case, doctor,



GG11 1
2 were you quoting to us those levels in nanograms or
3 nanomoles?

4 A. Those I believe are
5 nanomoles per ml.

6 Q. I don't purport to be able
7 to do those conversions as quickly, undoubtedly, as
8 you can, doctor.

9 THE COMMISSIONER: A little higher.

10 THE WITNESS: Nanomoles per ml are
11 slightly higher.

12 MS. CRONK: Q. Doctor, then in
13 respect of that child, I believe you said in evidence
14 that there did not appear to be any evidence of renal
15 difficulty or renal malfunction.

16 A. There did not appear to be,
17 no.

18 Q. Were you addressing your
19 mind, when you gave that answer, to the issue of
20 excretion ability or to tissue death in either the
21 kidney or the liver?

22 A. Here the issue was that
23 we have no evidence of renal or hepatic disease. We
24 had significant evidence of skin disease, and the
25 question then was what role digoxin present in the
patient's skin might contribute to the elevation or



GG12 1
2 persistence, shall we say, of the level in the
3 child's serum.

4 Again, that is not the only
5 possible explanation. Again we don't understand
6 the pathophysiology. But again we have a situation
7 where the level persisted despite the fact that
8 we would fully expect, with normal renal function,
the level to have come back down.

9 Q. And because the child,
10 insofar as you are aware, is still alive and no
11 autopsy was performed --

12 A. Yes.

13 Q. -- you can't help us as
14 to whether or not in fact, it was kidney, liver
15 or cellular death?

16 A. No. Except we had at
17 least blood level evidence that enzymes were normal
18 and creatinine was normal and urine output was normal
in the child. There was no clinical evidence of that.

19 Q. And the excretion function
20 appeared to be normal?

21 A. That is correct.

22 Q. All right. Thank you,
23 doctor.

24 Doctor, you have told us as well of
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a number of instances of medication errors as distinct from elevated ante mortem digoxin levels.

A. Yes.

Q. And you have told us of course, there was the experience on the neonatal ward, 7F, in January of 1982.

A. Yes.

Q. We have heard much about that.

A. Yes.

Q. The confusion of epinephrine for Vitamin E.

A. Yes.

Q. That was the situation as I understand it. doctor, where the bottle, or the container for each of the drugs was very similar; am I correct in that?

A. The two bottles of racemic epinephrine and Vitamin E, yes.

Q. And as well, doctor, as I understand it, there was no other labelling on either of the drugs to distinguish them from each other?

A. There were the names of the drugs.

Q. I'm sorry, apart from that, there was no indication that would make either



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distinct from the other, other than the names of the drugs?

A. The names, the labels, the indications, how to use them; all were different. The labels themselves, colourwise, and bottle size-wise looked remarkably the same.

Q. And as well doctor, I take it, at least it is my understanding, that both the drugs involved had the same logo and the same colour design?

A. Yes. They had a similar stripe type pattern on them.

Q. And I take it then, doctor - and once again we have heard evidence from yourself and others in this regard - that once there appeared to be an outbreak of illness amongst the children on that ward, there was an in-depth and detailed investigation that was undertaken virtually immediately.

A. Yes.

Q. And in addition to the experience on the neonatal ward, you have told us there were three patients on that ward in whom digoxin levels were recorded, although digoxin had not been prescribed.

Do I have the number correctly, that



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there were three?

A. No. I believe on that ward - again, I would have to go back to be sure - there was either one or two on that ward and several on 4A as well subsequently.

Q. Doctor, well in terms of the specific examples to which you drew our attention, your attention as well was drawn to page 178 of Mr. Justice Dubin's Committee's Report, and it is there indicated - just to refresh your memory, doctor:

"In addition to the medication error relating to epinephrine, the investigation disclosed that digoxin levels were detected in three patients in neonatal ward 7F for whom digoxin had not been prescribed."

A. Yes.

Q. Do you recall that, so we are talking about the same three?

A. Yes. And there had been subsequent patients within the Hospital as well.

Q. All right. We will come to those. At the moment, I am concentrating on the ones you drew to our attention.



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A. Yes.

Q. And of those three doctor,
as I understand it, the digoxin levels on two were
less than .5 nanograms.

A. Again I have not reviewed
those data, so I assume they are correct.

Q. Before I put the book down
may I continue, again at page 178 of the Dubin Report:

"Two of the levels were under .5,
which level was considered to be
unreliable, one disclosed a level
of 1.3."

Now, I will come back to the 1.3
level but for the moment, do you have any reason
to quarrel, or any information that leads you to
think that is a misstatement in the Dubin Report that
two of the three were under .5?

A. I would assume that is
correct, yes.

Q. And in respect of those
two doctor, I take it that those levels are well
within the range that has been reported in some of
the recent literature for the neonates and substance X?

A. One must be concerned when
one gets down to that level that one might not be



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measuring in fact digoxin, yes.

Q. And that is certainly one possibility, because the level is very low?

A. Yes.

Q. And the other possibility is that it might be substance X in a quantity that has been reported, for example, in Dr. Secombe's Vancouver setting?

A. Yes.

Q. If we turn then to the third case of the three children where the level of 1.3 was recorded, we have heard in evidence from other witnesses doctor, that there is perhaps some doubt as to whether or not that was in fact a medication error.

A. Yes.

Q. And to help you in that regard, I am referring to the early evidence of Dr. Soldin, which appears in Volume 8 of our transcripts at page 1329, and, briefly, doctor, he was asked this:

"Q. Can you help me, sir, as to whether, as the person who supervised these tests, you have any knowledge as to whether that 1.3 reading occurred as a result of a



1
GG18 2 medication error, as suggested in
3 this portion of the report..."

4 I was referring, as it happens to the same page in
5 the Dubin Report.

6 His answer was:

7 "A. No. It could have been
8 as a result of a medication error
9 but it need not necessarily have
10 been as a result of a medication
11 error."

12 "Q. Are you satisfied, sir, that
13 it was or do you have any knowledge
14 as to that?"

15 "A. No. I think that in the
16 light of information which we have
17 today, that it could well be that
18 that was not as a result of a
19 medication error."

20 I take it, doctor, given your
21 familiarity with the recent literature and, in parti-
22 cular, the reported case reports on studies of
23 substance X, that those are comments with which you
24 would agree?

25 A. One must be concerned,
certainly, yes.



GG19 1
2 Q. It is possible it was a
3 medication error?
4 A. Yes.
5 Q. Equally, it could be
6 another instance of substance X being reported within
7 the range of levels that were recorded at least
8 by Dr. Seccombe as well as others?
9 A. Yes.
10 Q. Then we come to the case
11 of Kristin Inwood, doctor, and you drew our attention
12 to that. We know, in that situation, that that
13 child through a mistake received a dose of
14 digoxin on March 12th at 5:30 a.m. that was intended
15 for another patient.
16 A. Yes.
17 Q. And in that case, if I
18 have it correctly, the error was discovered in due
19 course and indeed early the next day an incident
20 report was filed.
21 A. Yes.
22 Q. Do I have that correctly?
23 A. Yes.
24 Q. And in respect of that
25 particular dose, the baby apparently didn't suffer
any adverse effects.



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A. That is correct.

Q. Doctor, do you know how many incident reports were filed at The Hospital for Sick Children during the nine months with which this Commission is concerned - July of 1980 through March of 1981?

A. No, I don't.

Q. I take it you are not aware doctor of any incident report with respect to Justin Cook, Jessie Belanger, Stephanie Lombardo or Jordan Hines?

A. I am unaware of such.

Q. And in all those cases, doctor, those four cases - and I would like you to be clear about this; we are talking Justin Cook, Jessie Belanger, Stephanie Lombardo and Jordan Hines - in each of those cases we have heard digoxin was found by the Centre for Forensic Sciences in the tissues of each of those children.

A. Yes.

Q. You are aware of that?

A. Yes.

Q. And you told us that in the case of Justin Cook, given all the circumstances, in your opinion there is no other reasonable



1
GG21 2 explanation as to how an excessive amount of digoxin
3 resulted in this baby except by administration; do
4 I have that correctly?

5 A. Yes.

6 Q. We must accept then that
7 this child recieved an excessive amount of digoxin
8 and the issue becomes how that happened.

9 A. Yes.
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Q. And you have told us

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that you think it is reasonable, as I understand it,

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Doctor, that it could have happened either through

5

mistaken administration?

6

A. Yes.

7

Q. And you have suggested that

8

it is a reasonable possibility that it could have been
a medication error?

9

A. Yes.

10

Q. Or alternatively you cannot

11

rule out as a prudent scientist the possibility of

12

deliberate administration?

13

A. Yes. Nor can I rule out

14

that some may have been error and some may have been
intentional.

15

Q. Or a combination of the

16

two?

17

A. Yes.

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Q. Doctor, with respect to

19

the other three children, however, as I understand

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it, you have not reviewed the charts of any of those
three in any detail?

21

A. No, I have not.

22

Q. All right. You are not

23

aware then in those cases which medications were

24

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2 prescribed for those children, at what times or with
3 what relationship and point of time to the date and
4 time of their death?

5 A. This is correct.

6 Q. All right. I take it then
7 with respect to those three cases, Doctor, you have
8 told Mr. Lamek and others that at least those three
9 in your mind must fall into the medication error
10 category because digoxin was found in their tissues
11 when it wasn't prescribed for them?

12 A. They fall into one of
13 three possible categories. Each of them could be
14 either an error or intentional.

15 Q. Yes.

16 A. Or, as we said, perhaps
17 a phenomenon that we will learn about over the next
18 numbers of years with respect to substance X, if you
19 will.

20 Q. All right. But in respect
21 of at least the first two possible explanations, both
22 contemplated administration of the drug?

23 A. Yes.

24 Q. All right. Justin Cook is
25 the fourth that falls into that category?

A. Yes.



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Q. Can we deal then for a moment specifically with Justin Cook. We know, Doctor, that the arrest was called at 4:20 a.m., that is the arrest per se?

A. Yes.

Q. And that the associated events with respect to the arrest began at 3:45 a.m.?

A. Yes.

Q. All right. The child subsequently was pronounced dead at 4:56 a.m.?

A. Yes.

Q. As I understood your discussion with Mr. Hunt this morning you indicated that when we are looking at the events that took place during the arrest of the child we should quite properly consider those events that immediately preceded the calling of the Code 25?

A. Yes.

Q. Do I have that correctly?

A. That is correct.

Q. So, we are looking then at the events that commenced at 3:45 in the morning, proceeding through until the child was pronounced dead at 4:56 a.m.?

A. Or conceivably events



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prior to that.

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Q. All right. But for the

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moment I am talking about the arrest situation?

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A. Yes.

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Q. And that at the earliest

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it commences at 3:45 and proceeds through to the
time the child was pronounced dead?

8

A. Yes.

9

Q. Now, Doctor, if we

10

hypothesize that a medication error occurred at

11

or immediately before the time of arrest, the key

12

time then to look at, at least in the first instance,
is 3:45, either before that or some time after that.

13

Do I have that correctly?

14

A. Yes.

15

Q. All right. Can we deal

16

then first, Doctor, with the situation of the

17

possibility of a medication error some time after the

18

Code 25 was called?

19

A. Yes.

20

Q. Now, the Code 25 was called

21

at the time the arrest per se was called, that is
4:20 a.m.?

22

A. Yes.

23

Q. And that situation, Doctor,

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25



1
2 assuming that there was an accidental administration
3 of an adult ampoule of digoxin there would I suggest
4 to you have to be a series of mistakes that were
5 made that early morning on the ward.

6 A. Yes.

7 Q. The first is that digoxin,
8 having regard to the fact that it is a Code 25
9 situation would have to be present on the crash
10 cart, although that was not normally the case.
11 That is the first thing that would have had to have
12 happened, correct?

13 A. If all the drugs used were
14 present on the crash cart and no one had to get any
15 other drugs, I don't know that.

16 Q. All right.

17 A. But that can be established.

18 Q. I will come in a moment,
19 Doctor, to the scenario where perhaps someone had
20 to retreat back to the medication cabinet and the
21 general supply room on the ward, but I take it that
22 we can agree that in most resuscitation situations
23 the immediate supply of drugs is the crash cart,
24 indeed, it is intended for that purpose?

25 A. That is its intent, yes.

Q. All right. So that in this



1
2 situation, if a drug error was made, in the case of
3 Justin Cook, at the time after the Code 25 was called,
4 the first thing that needs to be there is digoxin
5 has to be on the crash cart?

6 A. Yes.

7 Q. All right. Secondly,
8 Doctor, it would have to be under your hypothesis
9 an adult ampoule of digoxin and not a paediatric
10 ampoule?

11 A. Yes.

12 Q. Do I have that correctly?

13 A. That would be probably.

14 Q. All right. Well, I am
15 sorry, Doctor, would it be necessary under your
16 suggestion as to how this child might have died?

17 A. With the assumptions of
18 accumulation in tissue probably, yes.

19 Q. All right. Well, I do
20 have ---

21 A. I would have to argue
22 that again, given both the tissue as well as the
23 serum concentrations it becomes very unlikely that
24 a paediatric ampoule could produce the results that
25 we obtained.

Q. All right. So, to



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produce the kinds of results that we have seen both in the serum post mortem and in the tissues, you have told us that that would require one adult ampoule of digoxin?

A. Yes.

Q. All right. So that assuming digoxin was on the crash cart, although it shouldn't have been there?

A. Yes.

Q. It would have to be that kind of digoxin, an adult ampoule?

A. Yes.

Q. All right. And then, thirdly, Doctor, I suggest to you that the nurse providing the drug, or drawing it up, had to make obviously the mistake of mistaking the digoxin for some other drug which an attending physician had ordered?

A. Yes.

Q. All right. Fourthly, Doctor, I suggest to you that Dr. Costigan and Dr. Mounstephen, who we know earlier at about 11:00 p.m. on the Saturday evening had taken an inventory of the drugs on the crash cart, would have had to have made a mistake and missed at least, at least one



8 2 ampoule of digoxin on the crash cart?

3 A. Yes.

4 Q. That is another mistake?

5 A. Yes.

6 Q. Right. Then, Doctor, I
7 suggest to you that regrettably there is another
8 and, that is, that the physician who administered the
9 drug after the nurse or the resident who drew it up
10 either had to not check it at all or check it
11 improperly, one of those two mistakes had to be made?

12 A. Yes.

13 Q. And I suggest to you,
14 Doctor, that that combination of errors, that number
15 of errors by that number of individuals is an
16 unlikely sequence of events. Can we agree on that?

17 A. I would suggest that if
18 a vial were inadvertently missed and somehow managed
19 to find a way onto the crash cart, by intent or by
20 accident, that the rest of the scenario then becomes
21 not at all unlikely.

22 Q. Well, Doctor, I understand
23 that. It may be Doctor that ---

24 A. In other words, the initial
25 issue sets in motion all the remainder of the
problems, including misreading, misinterpretation



1
2 and administration.

3 Q. Well, I understand,
4 Doctor, that the problem doesn't arise, at least
5 the possibility of medication error during that
6 time frame doesn't arise at all if the digoxin is
7 not on the crash cart?

8 A. Yes.

9 Q. So, I accept and agree
10 fullheartedly with you that if it's not there none
11 of the rest follows, but if it is there then you
12 have got a series of mistakes of one kind or another
13 by a number of separate and discrete individuals
14 that have to occur. Can we agree on that?

15 A. It could all result from
16 in essence one error, picking up the vial and drawing
17 it up into the syringe.

18 Q. All right. And we have
19 an error by the person drawing it up?

20 A. Yes.

21 Q. We have an error by Dr.
22 Costigan and Dr. Mounstephen the evening before?

23 A. Yes.

24 Q. We have an error by the
25 doctor in missing a vial of digoxin?

A. We can't have him missing



1
2 it because it's there, that's the same error.

3 Q. All right, Doctor, I
4 won't quarrel with you on the numbers.

5 A. The issue being, again,
6 and my concern is, with respect to that that if a
7 vial were missed, and it doesn't take much to miss
8 a vial particularly at 1:30 in the morning under
9 circumstances of doing a job which you are not
10 normally used to doing, pharmacists normally do
11 inventories and check drugs, this is late at night
12 after a tense difficult meeting, I am postulating
13 that to miss a vial is not at all an unlikely scenario
14 and that if that vial ended up being there then the
15 possibility of all the rest becomes rather probable
16 in fact.

17 I also suggest on the other hand,
18 and it is something that we have to take into
19 consideration, that somebody put it there to be used.

20 Q. All right, and that is
21 another possibility?

22 A. That's another possibility.
23 And it could have been put there under a variety of
24 circumstances again.

25 Q. Doctor, I wish to put it
no higher than this, and, that is, that if an ampoule



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2 of digoxin was on that crash cart because it was
3 missed the night before or because, as you have
4 now suggested, someone put it there deliberately
5 with the intent that it be used?

6 A. Yes.

7 Q. After that specific event,
8 there are a number of other events or opportunities
9 when that could have been corrected or detected.
10 Am I correct?

11 A. Certainly, true.

12 Q. Before that drug reaches
13 the child?

14 A. And I wouldn't be surprised
15 if all of them were missed because in every error
16 that is made in an arrest all of those same mistakes
17 have to be made. Every time somebody says give me
18 an amp of calcium and they substitute epinerphrine,
19 the exact same scenario occurs. The person who
20 picked it up has to misread it, they have to load
21 it into the syringe, they have to hand it to somebody
22 who administers it, who doesn't look at the vial
23 and all of the same errors apply. In fact, they
24 happen and they happen with a frequency that no one
25 can estimate, but certainly with a very real frequency.

26 Q. All right. Doctor, may



Spielberg, re.dr.
(Cronk)

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we look now at the time frame immediately preceding
the calling of the Code 25?

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A. Yes.

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Q. And as I understand it,

6

in that situation, again, we need several circum-
stances. First of all, we are not talking about

7

the crash cart in that scenario, we are talking about

8

access through the medication cupboard on the ward.

9

Am I correct on that?

10

A. Yes, and other wards.

11

Q. And other wards.

12

A. Because drugs were borrowed.

13

Q. All right. Doctor, under

14

that scenario then we need at least this event, someone

15

in the first instance has to mistake digoxin in the

16

medication cupboard for another drug that has then
been ordered or prescribed. Do I have that correctly?

17

A. Yes.

18

Q. All right. And that would

19

have to take place, at least if the drug came from

20

the medication cabinet on Ward 4A, 4B at a time when

21

we have heard from the evidence of Dr. Costigan that
all the digoxin on the ward was to be locked up and

22

that he at least witnessed the team leader with the

23

key in her hand about to do that before he departed

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from the ward. It is in that situation that has to
be done?

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A. Yes.

5

Q. And then thirdly, Doctor,

6

there would have to be a mistake made in a situation

7

where a drug had been prescribed for Justin Cook

8

because we are not talking yet about the events of

9

reason someone requested a drug for him and that

10

drug that was requested was mistaken for digoxin

11

was mistaken for that drug. Someone has to have a

12

reason to go to the medication cupboard, someone has

13

asked for a drug for Justin Cook?

14

A. Yes, as they were asked

15

to leave the ward and bring back propranolol or they

16

were asked to obtain morphine from the same cupboard
presumably in which the drug was kept.

17

Q. Doctor, I am conscious

18

of the time, so, I would ask you to accept for me

19

that the medical record of Justin Cook indicates that

20

from 2300 hours on the Saturday evening, that is

21

11 o'clock at night until 2:30 a.m. the child is

22

recording as having slept well with his respirations

23

appearing to be easy and regular. So, it would

24

appear during at least that time interval until

25



1
2 2:30 no medication was administered nor called for
3 for that child?

4 A. This presumably would be
5 case, yes.

6 Q. All right. Similarly,
7 Doctor, from the period of 2:30 through to 3:45 a.m.
8 there is a note in the progress notes of the child's
9 chart by Nurse Susan Nelles indicating that the child
10 had settled well after the 2:30 a.m. feeding, was
11 resting comfortably until about 3:45 a.m. when the
arrest appears to have started?

12 A. The blue spell began, yes.

13 Q. All right. So, we are now
14 at the period then from 11 o'clock on the Saturday
15 evening through right until 3:45 and it doesn't
16 appear that any medication was either ordered or
prescribed for the child?

17 A. I believe that is the
18 case, yes.

19 Q. All right. That takes
20 us then, Doctor, to that short interval of time
21 starting at 3:45 until the calling of the Code 25
22 at 4:20 when a medication error might have taken
place?

23 A. Yes.
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Q. And in that situation, Doctor,
we know that there were a number of drugs called
for for that child?

A. Yes.

Q. And according to the chart,
administered but possibly not, the medication error
occurred.

A. Yes.

Q. The first was Inderal.

A. Yes.

Q. The second was atropine.

A. Yes.

Q. The third was morphine?

A. Yes.

Q. Do you recall that?

A. Yes.

Q. And, Doctor, you have shown us,
at least Mr. Roland was good enough this morning to
introduce photographs of those various drugs. I
would simply show you two of them, Exhibit 228-D
and Exhibit 228-C.

A. Yes.

Q. And I think it is clear, Doctor,
from looking at the ampules of those two drugs which
appear in the photographs, that those of Inderal are



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very clearly a brown colour.

3

A. Yes.

4

Q. Whereas those of digoxin are

5

a clear liquid in a similarly shaped ampule.

6

A. This is correct.

7

Q. All right. And if we look at

8

the vial of morphine that appears in the picture, it appears to be the same shape.

9

A. Yes.

10

Q. As an ampule of digoxin, but

11

the lettering on it, or at least the printing on it appears to be a distinctly different colour.

12

A. Yes.

13

Q. Do I have that correct?

14

A. That is correct, the literature

15

being filled, literally filled with mistakes between

16

similarly and differently coloured vials and

17

different coloured lettering. In fact, to the extent

18

where people have begun giving up on the issue of

19

trying to colour code drugs with the only recommenda-

20

tion being that people have to read labels because

21

colour coding does not prevent errors.

22

Q. I don't doubt for a moment,

23

Doctor, that there are all kinds of errors where in

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fact that happens. My suggestion only is that in this

25



1
2 situation, if one postulates, as one of the counsel
3 in the room did this morning, that digoxin was
4 mistaken for Inderal, you at least have to have the
5 mistake first that the digoxin was mistaken for
6 Inderal and, secondly, that a clear ampule of a drug
7 with different coloured labeling on it was
8 mistaken for a brown coloured ampule of drug
9 with different lettering on it. That has to have
10 occurred as well.

11 A. It is the same thing.

12 Q. Well, all right, Doctor.

13 MR. ROLAND: Well, to be fair to the
14 witness and to the evidence, my friend isn't being
15 quite fair, I don't think, in dealing with Inderal
16 because, as I understand the evidence, it appears
17 there were some syringes that were taped to the
18 bed and there may or may not have been a vial with
19 those syringes, we don't know that from the evidence.
20 So that to put it as my friend does doesn't do justice
21 to the evidence.

22 MS. CRONK: I'm sorry, sir, I am coming
23 to the question of syringes. I was addressing my
24 mind only to the confusion of ampules in the medica-
25 tion cupboard. I thought the scenario
I had given was that someone had gone to the medication



4 2 cupboard.

3 A. The Inderal was not in the
4 medication cupboard on that ward.

5 Q. And where was it kept on the
6 ward?

7 A. It wasn't on that ward, it was
8 obtained from another ward.

9 Q. All right.

10 A. At least, that is the testimony
11 that has been provided.

12 Q. So, there was no Inderal on
13 that ward at all that night?

14 A. I have no idea if there was
15 propanolol on that ward but that propanolol
16 appears to have been sought from another ward,
17 presumably because either the ward was out or for
18 reasons that I don't understand.

19 Q. Doctor, as Mr. Roland points
20 out, and indeed it has been discussed this morning
21 there is the issue of whether or not a preprepared
22 syringe, and I am not going to try to say the trade
23 name of it, of Inderal, was in fact attached to the
24 child's bed?

25 A. Yes.

Q. And I merely suggest this to



1
2 you, that given that the drug had to be mistaken,
3 that digoxin had to be mistaken for the drug, that
4 if that syringe was used and it contained not as
5 intended Inderal but rather digoxin, then the physician
6 who administered it had to fail to make an inquiry and
7 to check what the contents of the syringe was or,
8 alternatively, if it was administered not using a
9 syringe had to fail to check the ampules. Is that not
10 a fair scenario of what would have had to have
happened?

11 A. At a very reasonable scenario,
12 yes.

13 Q. All right. Thank you, Doctor.
14 Then, Doctor, as I understand it, you
15 have indicated with respect again to the question of
16 a medication error, in the case of Kristin Inwood,
17 that you have two concerns, at least, amongst others.
18 The first concern, as I understand it, centers upon
the sample that was taken.

19 A. Yes.

20 Q. And with the assistance of Mr.
21 Roland it has been established that that sample was
22 apparently taken at the postmortem of that child.

23 A. Yes.

24 Q. And that it was a blood sample
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which, when ultimately sent to the Centre of
Forensic Sciences, was a serum sample. Is that
your understanding now on the basis of what has
been established thus far?

A. Yes, not an unprocessed
sample.



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Q . Doctor, are you familiar with the procedure in the Pathology Department at the hospital whereby in a non-medical legal case the resident, the attending pathology resident, rather than the staff pathologist, carries out the autopsy?

A. I am not familiar with the procedures in the Department of Pathology.

Q. To help you, Doctor, we have had evidence in that respect from Dr. Cutz and Dr. Mancer, staff pathologists from the hospital, and it appears from the preliminary autopsy report on Kristin Inwood that Dr. Glen Taylor, then a resident pathologist, and Dr. Phillips were responsible for the signing of the preliminary autopsy report and the conduct of the preliminary autopsy.

Doctor, Dr. Taylor testified when he appeared before the Commissioner, and this appears, sir, at Volume 43, Page 8745, he was asked this question:

"Q. Now, doctor, if I understand it at a routine autopsy, when there is a request made or it is desired to take a sample of blood, the usual place is the inferior venal cava;



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is that so?

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A. That is a convenient place and,
therefore, it is a usual place, yes.

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Q. And that is actually a vein
leading into the heart?

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A. A large vein leading into the
heart, yes."

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My question to you, Doctor, is this: if Dr. Taylor,
in the instance of Kristin Inwood, followed his normal
practice and drew the sample from the inferior
vena cava, would you have then less concerns about
an artefact in that sample resulting from the method
of sampling as opposed to any other problem?

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A. The first point, scientifically
not knowing where it came from, I really cannot
comment. If it came from that side and as the heart
exhibited myocardial necrosis and capillary
muscle necrosis, that still could contribute
significantly to digoxin concentrations being pumped
from the heart to other organs.

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If it came from the heart, I would be
even more concerned because in fact it could have
been drawn very close to that dead piece of tissue.
If it were drawn at another site, I would still be
concerned because that phenomenon had occurred in that



particular child, even if it was, for example, from sagittal sinus.

Q. Doctor, of all those available sites from which the sample might have been taken, and I understand well what your concerns are if it was drawn directly from the heart given the muscle difficulties that had been accounted in the child, I am asking you to assume in light of Dr. Taylor's evidence that the sample was in fact drawn from the inferior vena cava. Would you make that assumption with me for the moment?

A. Yes.

Q. My next question to you then is, Doctor, are you familiar with the practice in the Pathology Department and about this we have heard other evidence, that when a sample of blood is taken for virology or bacteriology purposes, the sample site is first sterilized by the application of a hot instrument to sear the surrounding muscle site around the vein from which the sample is taken. We know that on occasion that happens.

A. Yes, I have seen such procedures done, yes.

Q. I ask you, then, to assume that in this case the sample was taken from the inferior



4 2 vena cava and because it was taken for virology
3 purposes by Dr. Taylor that that sterilization
4 procedure was followed. In those circumstances,
5 Doctor, would you have less concern that an artefact
6 had resulted in the sample from the way the sample
7 had been taken as opposed to any storage issue?

8 A. I might be more concerned. I have
9 no idea what the effects of burning tissue might
10 have on release or non-release of digoxin.

11 Q. One way or another?

12 A. One way or another.

13 Q. Okay, that is fair, Doctor.

14 A. One might be -- actually, I was
15 unaware that that would be done with a vein
16 preparation. One of the things that one might be
17 concerned about is in fact, depending on how the
18 syringe is held, if you begin drawing back, putting
19 some negative pressure on the syringe as you enter
20 the wall of the vessel to get into the blood cavity,
21 in other words, do not go straight into the blood
22 cavity and then draw back, and you have just seared
23 tissue, the possibility exists in fact that you might
24 end up having tissue juices around which you
25 would then pick up in the syringe as you drew back
and entered the chamber.



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2 The same applies, of course, for the
3 heart, and very often the way in which you do a
4 cardiac puncture is by providing negative pressure
5 so you know when you enter the chamber. If you
6 pre-seared the muscular wall of the vessel, that
7 becomes another source of concern to me. I have
8 no data one way or the other.

9 Q. But it is certainly an issue
10 that you would address?

11 A. It is a concern that in fact
12 could be addressed, at least in part experimentally,
13 but given again the variations in which these things
14 are done, it has to be a source of concern, yes.

15 Q. Then I will have to have further
16 evidence from the pathologists involved as to how
17 they took that sample, Doctor, and what the
18 procedures were that were followed?

19 A. Yes.

20 MS. CRONK: Sir, I am conscious of the
21 time. I will be about another ten minutes. May I
22 have your indulgence to continue?

23 THE COMMISSIONER: Yes.

24 MS. CRONK: Q. With respect still
25 to the case of Kristin Inwood, Doctor, and quite
apart from the problem related to the sample, as



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2 I understand it -- well, first, you have suggested
3 in that case as well that it is possible that
4 a dose of digoxin was mistaken for a dose of
5 lasix intended for the child, that that is a
6 possibility?

7 A. Yes, or given at any other time
8 as another child's medication or whatever, but that
9 is one potential time when the dose might have been
10 given.

11 Q. That was an opportunity for
12 medication error, as I think you described it?

13 A. It was a clearcut
14 opportunity.

15 Q. And, Doctor, were that the case
16 and were a medication error to have been made at that
17 time, that is really the fifth out of the eight
18 children that we have been talking about where
19 a medication error might have been, in your mind,
20 a real possibility.

21 A. Or the fifth out of 10,000 some-
22 odd doses administered on the ward. We have to be
23 very careful in looking at numbers. We are talking
24 about now tens of thousands of doses being
25 administered and I do not know how to solve the
problem epidemiologically. Obviously, that has to



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2 be dealt with by somebody more sophisticated in those
3 matters than I, but we are dealing with literally
4 tens of thousands of doses, some of which might
5 find their way into errors. For example, when we
6 are talking about an incident report, that probably
7 represents a thousand errors based on the literature,
8 anyway, one incident report per thousand error
9 actually gets filed, and as such, one has to be
10 terribly concerned about that possibility, and we worry
11 about it all the time, clinically, and I cannot view --
12 at least I cannot find an easy way of viewing four
13 patients or five patients or six patients in one
14 group as opposed to the 10,000 doses administered
15 to other groups without knowing what happened to the
16 rest of the population as a whole.

15 Q. I understand, Doctor, the
16 concerns relate both to the number of doses that might
17 have occurred with respect to these children as
18 compared to the total number of doses.

19 A. Yes.

20 Q. And as well, in the context of
21 the children whose deaths are under review by this
22 Commission, you, in your evidence, had talked about
23 eight of them, and Inwood would be the fifth, by
24 my count, and I may be wrong, where we have to
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address the possibility in your opinion of a medica-
tion error. That is all I was suggesting.

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A. Exactly, and it must be addressed.

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Q. All right. Doctor, in respect
to the case of Kristin Inwood, and I understood in your
discussion with Mr. Roland yesterday, you suggested --
at least he suggested to you and you agreed that at
the top of the alpha curve, if that was the timing
of the child's death, it would amount to about
two and a half adult vials of digoxin that would have
had to have been administered to the child to result
in a postmortem blood level of 491 nanograms; did I
understand that correctly?

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A. I would have to go back to the
exact numbers. That was assuming that the drug has
now left circulation and has entered the central
volume of distribution.

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Q. No, I had understood it the
suggestion being the top of the alpha curve.

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A. The top of the alpha curve is
after the drug has left circulation and entered the
central volume of distribution with a volume of
distribution of approximately from .6 to 1 litre
per kilogram. That was the basis of that calculation.

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Q. All right, Doctor, and in that



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2 situation, as I understand it, your evidence is
3 that as best you can determine and on the informa-
4 tion that is available to you, it would require
5 at that stage 2-1/2 vials, adult vials of digoxin
6 in order to achieve levels that high; do I have
7 that correctly?

8 A. Yes, to achieve the level
9 immediately with subsequent arrest, requiring less
10 than one adult vial.

11 Q. But I would like to deal for
12 a moment with the other situation that you postulated
13 and that is that an error with that kind of timing
14 would require 2-1/2 vials?

15 A. Yes.

16 Q. As I understood your further
17 discussion with Mr. Roland, and I want to be clear
18 that I understand this, you said that if that was
19 the dose, if we were talking about that kind of
20 timing, that amount of digoxin, we were probably
21 talking about, in your words, rather rapid administra-
22 tion by IV push; do I have that correctly?

23 A. That is the most likely scenario.
24 Again, one could build pharmacologically other
25 potential scenarios, again, the problem being the
nature of kinetics. One could design other scenarios.



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Q. But in your opinion, that is the most likely?

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A. That would be a very reasonable way to achieve that kind of level, probably the most reasonable if we are talking about those kinds of numbers of vials. To achieve levels that high in other ways requires administration of, again, far more vials.

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Q. Well, let us deal just with the one that is not beyond, in your view, the realm of possibility, the 2-1/2. That, you told me, the most probable method, then, would be a rapid IV push?

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A. We are still mixing apples and oranges a little bit.

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Q. Perhaps to be fair to you I will read you the question and the answer to anticipate my friend, Mr. Roland.

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A. Okay, my calculations, which I believe I said the least amount was .047

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micrograms at no continued distribution even out of circulation, a central volume of distribution

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at the top of the alpha curve, if you will, of 1.27 milligrams, which is about 2-1/2 adult vials

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with a maximum being somewhere in the neighborhood of

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18 milligrams. These are the calculations which I believe I read during that time.

Q. Well, the only reason that I was confused, Doctor, and I may have another quote as well, but in an exchange with Mr. Roland, and this is in Volume 56 at Page 2441, the suggestion was made to you that I have just now repeated to you, that if the timing was that it was at the top of the alpha phase, it would require 2-1/2 vials of adult vials of digoxin, and you said yes, that was the case.

A. Assuming a volume of distribution of one litre.

Q. And then, as part of an answer to another question, you began to discuss the method by which that might have been accomplished, the route of administration?

A. Yes.

Q. And you said, as I understood it, this:

"Similar vials, reasonably urgent situation, and again, substituting that for the lasix and given in the mode in which lasix is normally administered, which is a very rapidly IV push,



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could well have accounted for both

the extremely high blood level

The potential of lack of distribution

in this infant, which we have to postulate

to expect the extremely high blood

level and her subsequent course."

And the only reason that I was a little confused

about that, and I just wanted to be clear, is that

I thought you were saying in the context of those

questions and that answer that were that the timing,

were that the amount of digoxin, the most likely

explanation in your mind is that would be administered

by a rapid IV push?

A. That is a very good hypothesis.

Q. All right, Doctor, and in that

situation with those three variables, as I under-

stand it, there is another problem also suggested

to you by Mr. Roland, and that is that death from

propylene glycol could set in within, as you

suggested yesterday, a matter of minutes?

A. Yes.

Q. Now, if that is the situation,

Doctor, we know in the case of Kristin Inwood that

lasix was administered at least as recorded

by the medical record, some time between 2 a.m. and



13 2 2:30 on March 13th.

3 A. Yes.

4 Q. And the reason for that is
5 that the arrest occurred at 2:30 a.m. and lasix
6 apparently was administered before that?

7 A. Yes.

8 Q. And death occurred at 3 a.m.?

9 A. Yes.

10 Q. Now, Doctor, if that is the
11 case, just on the pure mathematics of it, if we
12 assumed that lasix, or whatever the drug was, was
13 administered very shortly after 2:00, the child
14 appears to have lived for almost an hour after the
15 administration of that drug?

16 A. No, my understanding is that
17 the resident was called at approximately 2 a.m.
18 We do not know how long it took for the resident
19 to arrive.

20 Q. I understand that, Doctor. I
21 am going to suggest to you it was administered at
22 2:29, all right, just before the arrest, and I
23 asked you, I thought, to assume for the moment that
24 if it was administered shortly after 2 when the
25 resident first arrived, and that was an assumption,
there are a number of possibilities, that if that is



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2 when it happened that the child lived for
3 almost an hour because the child was pronounced
4 dead at 3 o'clock?

5 A. The arrest being at 2:30?

6 Q. At 2:30.

7 A. Yes.

8 Q. Then let us do the other
9 assumption, and that is that if the lasix or what-
10 ever the drug was was administered just before the
11 arrest, and we know it was done before the arrest,
12 that would make it just before 2:30 in the morning and
13 the child lived until 3, at least is pronounced
14 dead at 3 o'clock.

15 A. Is pronounced at 3 o'clock, yes.

16 Q. And, Doctor, in those
17 circumstances, my difficulty is this: It appears to me
18 that if we hypothesize that digoxin in those
19 quantities was mistaken for lasix and was
20 administered to the child, we have the child, first
21 of all having regard to the potential effects of the
22 glycol which you have told us about that reacts in
23 one or two minutes ---

24 A. Depending on the rate at which
25 it is administered.

Q. All right. And assuming, because



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you have told us that you think it most likely that digoxin in that quantity would have been administered by a rapid IV push, the difficulty I have is that that child appears to have lived too long by either scenario, either an hour at the outside or a minimum of 30 minutes.

A. The issue is that a push of propylene glycol or any other drug does not necessarily result in death. It could result, in fact, in an arrhythmia which would lead to a half hour long resuscitation.

Point one: when we said before distribution, that does not imply 2-1/2 vials; we said that this can be an adult vial, one, because it might still be in circulation or very poorly distributed at that point. The fact that a drug may produce toxicity very rapidly does not tell us how long a resuscitation attempt may go on. In fact, a resuscitation attempt may go on for a very long period of time in some situations with distribution of drug; in some situations without distribution of drug and with variables that we cannot possibly explain.



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27oct83 2 Q. I think then the area perhaps of
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DMra 3 my confusion doctor, related to the effects of the
4 propylene glycol.

5 MR. ROLAND: Mr. Commissioner, to
6 be fair to the witness, my friend said the child
7 lived another half hour and if you will look at the
8 arrest itself on page 62 of the chart, it says - it
9 is a short arrest note:

10 "No electrical response, no
11 response to CPR."

12 I don't know what my friend is
13 trying to get at, but at least I thought she would
14 look at the arrest chart and not give us the impres-
15 sion that the child lived another half hour.

16 MS. CRONK: I was relating that only
17 to the time at which the child was pronounced dead.
18 I think that is the worst and the best scenarios.

19 MR. BROWN: Mr. Commissioner, I
20 think there has been evidence before that the time
21 a child is pronounced dead is not the time the child
22 necessarily dies. There is an arrest and efforts
23 are made to resuscitate the child, but that does not
24 mean that the child has lived from the time of the
25 arrest to the time of pronouncement of death.

THE WITNESS: And in fact here.



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the chart indicates no response, no electrical
activity.

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THE COMMISSIONER: I suggest it is
only God that knows when that child died.

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THE WITNESS: Yes.

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MS.CRONK: Q. Well, doctor, then --

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A. The point again being that
propylene glycol injected rapidly will cause toxicity
very rapidly.

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Q. But not necessarily death?

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A. It depends what one defines
as a death event. If it produced a degree of
bradycardia that subsequently went on to further
bradycardia leading to the arrest, that is entirely
consistent with that type of toxicity. It will be
dependent on the nature of the patient's heart, the
rapidity with which the drug is administered, the
contents and amount of drug that is actually
administered, and the net clinical result might be
the onset of adverse events, very rapidly, but then
the time that those events are recognized or become
severe enough leading to the calling of a Code is
problematic and dependent on the staff on the ward
at the time. Then we have a child in whom, at 2:30,
we are told no electrical activity, no response to

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CPR.

Q. All right, then, doctor, do I have it that, in either situation, it is dependent upon two things - and by either situation, I mean whether it is one adult ampoule of digoxin or whether it is 2.5.

A. Yes.

Q. In either situation, it depends, first of all, on how fast that ampoule is, in fact administered?

A. Yes.

Q. And perhaps then when you describe a very rapid IV push, I was leading erroneously to the conclusion that would lead to the result of death within a few minutes. As you suggested yesterday, that might not be the case?

A. It certainly would lead to some manifestation of toxicity very quickly. Whether or not the child ended up dying of those toxicities immediately or ten minutes later.

Q. The child may not have --

A. -- one cannot predict.

Q. And that would depend, I take it, doctor, on the speed with which the drug was actually inserted?



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A. Speed, amount, the child's condition; all the other variables that would go into what the state of his vagal nerve is at that time, whether there is excessive vagal activity or decreased vagal activity.

Q. A host of factors?

A. A host of factors. But, again within reasonably brief time periods that we are talking about.

In other words, for example, onset of symptoms four minutes, five or ten minutes after a rapid injection, very consistent, or onset of symptoms very quickly with deterioration afterwards, again very consistent.

I don't mean, by focusing on this one point, to suggest this is the scenario. This is a possible scenario. There are many other possible scenarios. The point being that based on even this extraordinary level, we cannot assume either intent or accident or mechanism by which the digoxin was given. We have to consider a series of possibilities, this one being not a bad possibility - in fact, a good possibility because of the relative timings, the fact that a drug did have to be given and typically would be given with a reasonably rapid push. It is a



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good opportunity. Possibly the best opportunity.
Again, I can't say anything about motive. It is
possibly the best opportunity for intent.

Q. Doctor, leaving aside the
question of motive, I take it we can at least agree
this far, that it is clear; in part, I misunderstood
what you said yesterday?

A. Yes.

Q. That at least we have to
be concerned, whatever the amount of drug that was
administered, if an error took place and if it
occurred at the time when lasix should have been
administered --

A. Yes.

Q. -- we have to be very
conscious of the possible effects of glycol, if it
was given too quickly at that stage?

A. Yes. Again, because the
effects of the digoxin, in a general sense, will be
somewhat slower.

Q. And you have said that
a number of times.

A. Yes.

Q. Doctor, very briefly - and
this is the last area, having regard to the time - can



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we turn to the case of Allana Miller.

As I understood your evidence and your discussions over the last two days in respect of that child, once again you expressed some difficulty, as I understood it, regarding the method whereby the post mortem blood sample had been taken.

You said I believe, that you were not sure where the sample had been taken from. Do you recall that?

A. Yes.

Q. Because of that, you were concerned, first, as I understood it, that if it had been taken intracardiac, that would have a rather large effect in the calculation of the possibilities you were examining?

A. Particularly in light of the cardiac trauma, yes.

Q. And, alternatively, if it was taken from another site, that might still have a significant effect but you were in some difficulty because you didn't know where the sample had come from?

A. Yes.

Q. Doctor, I would like to help you with that if I could.. Dr. Cutz has testified - and this is found in Volume 44, sir, of our



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evidence, at page 8934 - that he was personally present when the samples were taken at the autopsy of that child --

A. Yes.

Q. -- that Dr. Taylor, the resident you spoke about a few moments ago --

A. Yes.

Q. -- drew the sample; that the blood was drawn by Dr. Taylor in Dr. Cutz' presence from the inferior vena cava, the usual site --

A. Yes.

Q. -- that he expected the usual sterilization procedures were undertaken before the sample was taken; that Dr. Taylor used a needle and syringe to draw the blood specimen.

A. Yes.

Q. Dr. Cutz finally testified on that issue that in his opinion, having regard to what he saw and the way it was taken, there was no risk, in his view, that the sample had been contaminated.

With those facts in hand, doctor, and they were provided to you in your earlier discussions, would you have any remaining concern as to the quality of that sample? It is clear it didn't



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JJ8 2 come from the intracardiac site.

3 A. Yes. Again the question
4 I raised with respect to that infant was how the
5 particular resuscitation events might have influenced
6 the blood levels achieved.

7 Q. Would that include possible
8 trauma to the inferior vena cava, doctor?

9 A. Not trauma to the inferior
10 vena cava but, rather, trauma to the cardiac muscle
11 with release of digoxin during that process.

12 Then, obviously, if the sample
13 were drawn through the heart, one might postulate
14 a greater probability of it having been influenced,
15 the level that is, by direct trauma to the heart.

16 However, if again during the
17 resuscitation process, we have continued and ongoing
18 damage to the heart with release of digoxin into the
19 blood, certainly, that released digoxin might - and
20 again we can't say with any degree of assurance; I
21 am bringing it up only as a question and something
22 we must consider - certainly, that increased digoxin
23 potentially released from cardiac muscle during the
24 resuscitation could readily find its way to the rest
25 of the circulatory system.

Q. Including the inferior vena



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cava?

A. Certainly.

Q. All right, doctor. Thank
you.

With respect as well to the death
of Allana Miller, quite apart from the issue of
the sample, we know now at least it didn't come from
the intracardiac site.

A. Yes.

Q. There are all the problems
associated with potentially it having come from the
inferior vena cava. Yet, you suggested in the case
of Allana Miller, as I understand it once again, that
there is a possibility, in your view not an un-
realistic one, that digoxin may have been mistaken
for lasix in that child's case as well?

A. Yes, that is one of the
possibilities.



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Q. And that was again because the drug had been prescribed Lasix, that was an opportunity for medication error?

A. Yes.

Q. Doctor, we have heard with respect to Allana Miller, at least on the progress notes of the medical record it appears that Dr. Soulioti administered, she is recorded as having administered Lasix by IV push at 2:40 a.m., that is page 32 of the medical record.

A. Yes.

Q. And 2:45 a.m. seizure developed, CPR was initiated, Code 25 was called.

A. Yes.

Q. And the child was pronounced dead at 3:27 a.m.

You suggested, Doctor, with respect to those events and the possibility of medication error, this is at Volume 56 Mr. Commissioner, page 2445, and this was with respect to Allana Miller Doctor.

A. Yes.

Q. "Then we have to deal with administration. Again, we express one possibility, that being a dose of drug given within five minutes of the child's



JJ2.2 1
2 "asystolic episode, a very short
3 interval from the administration of
4 Lasix to the arrest of the child.
5 That is one opportunity during which
6 either error or intentional substitution
7 of drug could have occurred. Again
8 remembering that when somebody asks
9 for a drug to be administered, a
10 physician, the drug is drawn up and he
11 is handed a syringe containing a liquid,
12 trusting in fact that it is the
13 compound that he wishes to give, or
14 that he has asked for."

15 And then there was an exchange between
16 the Commissioner and yourself regarding the checking
17 of the vial by the doctor.

18 A. Yes.

19 Q. And you said it varied during
20 urgent situations from yes to no. You said the rule
21 should be that somebody opens the vial, draws up,
22 shows the vial to the doctor, shows the syringe to the
23 doctor and injects it, particularly during urgent
24 circumstances that does break down, I have certainly
25 seen it happen it happens not infrequently.

A. Yes.



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Q. Doctor, if evidence were to be

led before the Commission that established that Dr. Soulioti had requested a nurse to fetch for her some Lasix, and that one of the nurses had brought an ampule to her that she then personally drew up 6 milligrams in a syringe and administered, what she described as Lasix to the patient pushed through the IV, if that evidence were to be led I take it your fears concerning the accidental substitution of digoxin for Lasix at least at that point in time would be reduced?

A. Reduced but certainly not gone.

I certainly have been in circumstances where a nurse has handed me medication telling me what it is, I believed looking at it quickly that is what it was, drew it up and then subsequently realized it wasn't.

Q. Yes, if that were to have

happened in this case Dr. Soulioti would have had to either check the vial too quickly and made an error, or failed to check it all despite the fact she was drawing it up into the syringe?

A. Yes, again very frequent events on the wards.

MS. CRONK: Thank you Doctor, it has been a very long four days and I have made it perhaps



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unnecessarily longer. Thanks for your patience.
Thank you, sir.

THE COMMISSIONER: Thank you. Thank
you, Doctor.

--- Witness withdraws

THE COMMISSIONER: Ten o'clock on
Monday.

MS. CRONK: For the benefit of other
Counsel our next witness is Dr. Phillips, the
Pathologist in Chief at the hospital.

THE COMMISSIONER: He is to be followed
by Dr. Bain, is that correct?

MS. CRONK: That is my understanding,
sir.

THE COMMISSIONER: I take it you have
no further comments?

MR. BROWN: No, I have not been able to
contact Mr. Sopinka, I will advise you on Monday.

THE COMMISSIONER: All right, thank you.

--- Whereupon at 5:30 p.m. the hearing was adjourned
until Monday, October 31st, 1983 at 10:00 a.m.

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